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Lastly, I want to thank the Wise Owl, who helped me through the dilemmas of statistics and data interpretation and watched over me during my writing up, steering me away from distractions and spurring me on.
**Declaration**

The work described in this thesis was undertaken whilst I was employed as a Clinical Research Fellow in the Department of Surgery, Glasgow Royal Infirmary between August 2006 and August 2008, under the supervision of Dr RF McKee and Prof P Horgan.

Except where otherwise stated, data interpretation and analysis has been performed by myself. The writing of this thesis was all my own work.

**Publications and Abstracts**


Hallum NS, McMillan DC, O'Reilly DSJ, Baxter JP, McKee RF. Longitudinal study of whole blood manganese levels in home parenteral nutrition patients over one thousand days and comparison with manganese dose, liver function and markers of inflammation. *Poster Presentation.* European Society of Parenteral and Enteral Nutrition. Florence 2008.

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## Chapter 1. Introduction

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Abstract

Background and Aims
Home Parenteral Nutrition (HPN) has been a major advance in the management of patients with gastrointestinal failure. It demands regular monitoring to ensure optimal intake, assess treatment response and minimise complications. The Scottish Home Parenteral Nutrition Managed Clinical Network (MCN) affords the opportunity to collect and analyse data about many aspects of HPN. The Network produced a guideline advising three monthly monitoring of biochemistry, micronutrients, vitamins, weight and anthropometry. This study firstly assesses the frequency and adequacy of monitoring of these complex patients and investigates any effect of this on complication rate. The second chapter is devoted to the outcome data of this geographical population and the comparison of survival figures to other intestinal failure (IF) centres. Lastly, hypermanganesemia is commonly reported during the follow up of HPN patients. Manganese (Mn) is added to parenteral nutrition in a multi trace element solution. Flexibility to alter the dose is limited. Manganese dosing and whole blood level is analysed to assess correlation. Other blood parameters are compared to assess any influence they may have on body manganese levels.

Methods
All patients receiving HPN funded by the NHS (National Health Service) in Scotland are known to the MCN via the National Contract for provision of HPN. Data is collected in an MS Access database. Data was extracted from this and absent information sought by personal communication.
Results

Monitoring of HPN patients across Scotland is performed regularly, however, only one third of patients met the 100 day standard. Consequences of this seemed negligible with no increase in complication rate of those reviewed less often.

Outcome data is broadly comparable to large UK IF centres. Overall survival at 5 years is 77.2%. Outcome is dependent on primary disease diagnosis with Crohns disease and motility disorders having the best figures. Cause of death for the majority of patients (65%) is purely disease related rather than as a complication of HPN.

Hypermanganesemia was found in 11 of 12 patients at least once during the study period. Whole blood manganese levels were not related to cumulative manganese dose, or blood parameters such as C reactive protein, ferritin or alkaline phosphatase.

Conclusions

It may be clinically viable and economically sensible to decrease the frequency of monitoring in HPN patients without detrimental effect. Complications are no more often found in patients reviewed with less frequency than those seen more often. A tailored approach to follow up and monitoring may be appropriate and is worth considering with respect to clinical workload and economic consequence.
Survival in our Scottish HPN patient population is comparable to that of tertiary UK centres and European equivalents, despite our wide and unselected geographical population and the logistical difficulties it presents.

Manganese levels are frequently high in our HPN patients. As yet, no convincing data exists to resolve the relevant clinical, biochemical or environmental factors. A multifactorial solution is anticipated.
Aims and Objectives

The first aim of this thesis is to investigate the monitoring of home parenteral nutrition (HPN) patients across an entire geographical population. All patients are monitored according to guidelines set by national nutrition experts. This study aims to determine whether Scottish HPN patients are meeting these targets. All aspects of monitoring will be analysed including routine blood tests, micronutrients and trace elements, anthropometry, and weight measurement. The guidelines are, to date, non-evidence based and a secondary aim of the study is to determine whether more infrequent reviews correlate with more complications warranting hospital admission.

Secondly, survival and outcome is to be analysed from this Scottish HPN population. All patients commenced on HPN since 2000 have been prospectively recorded on the purpose built HPN MCN data base and seven year follow up is now possible. This study aims to establish whether this population of patients behave in a similar way to previously reported groups in terms of survival, prognostic factors and HPN dependence.

Lastly, one particular trace element of current interest is manganese (Mn). Many studies have reported a high incidence of hypermanganesemia in HPN patients. Causes suggested have included dose of Mn prescribed, deranged liver function, intercurrent infection or inflammation, contamination of HPN feed and dietary contributions. This thesis aims to examine the behaviour of Mn in this Scottish population with regard to cumulative dose, markers of liver derangement and inflammation and dose in the past 7, 14, 21, 28, 56 or 84 days.
Chapter 1

Introduction

1.1 Intestinal Failure

The term Intestinal Failure (IF) emerged as a clinical entity over 20 years ago and was originally defined as ‘the reduction in functioning gut mass below the amount necessary for adequate digestion and absorption of food’ (Fleming, Remington 1981). A more recent definition states that intestinal failure occurs ‘when there is reduced intestinal absorption so that macronutrient and/or water and electrolyte supplements are needed to maintain health and/or growth’ (Nightingale 2001b). This later definition allows for those patients who simply require fluid and/or electrolyte support. A third, aetiological definition proposes that intestinal failure ‘results from obstruction, dysmotility, surgical resection, congenital defect or disease-associated loss of absorption and is characterised by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance’ (O’Keefe, Buchman et al. 2006). The condition can be of varied severity and duration. The acute cases tend to be of short duration, requiring artificial nutrition for between two weeks and six months and are managed in non-specialised units. Chronic or permanent IF is much less common than the acute version of the disease. A classification to cover the spectrum of pathologies has been devised. Type 1 intestinal failure is classified as self-limiting intestinal failure as occurs following abdominal surgery, necessitating short-term fluid or nutritional support, and usually resulting in a complete recovery without complication. Type 2 is intestinal failure in severely ill patients with major resections of the bowel and septic, metabolic and nutritional complications requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery. Type 3 is chronic intestinal failure requiring long-term nutritional support.
1.2 Aetiology of Intestinal Failure

Type 1 failure is a temporary consequence of abdominal surgery or other acute illness. Types 2 and 3 can result from a range of conditions affecting the gastrointestinal tract. The main causes have not changed since the 1980s when the two main intestinal failure units in the UK were set up. Crohn's disease is the most common underlying condition, followed by bowel ischaemia, motility disorders, malignancy and radiation enteritis. Post-surgical conditions such as intestinal fistula and chronic adhesive obstruction also feature, along with many rarer conditions (Irving 2000).

1.3 Home Parenteral Nutrition

The provision of Home Parenteral Nutrition (HPN) allows a release from the hospital environment for those patients unable to gain nutritional independence with adequate gastrointestinal function. It is a low volume – high cost life preserving treatment for patients with intestinal failure (IF), when neither oral nor enteral feeding is effective. It can be short term, to facilitate other treatments such as chemotherapy, medium term, with the intention of encouraging an adaptive response in those with short bowel syndrome (SBS) or whilst awaiting surgery, or long term in patients for whom absorptive capacity will never return.

1.4 Indications for Home Parenteral Nutrition

Short bowel syndrome is the best known form of IF. A comparison of indications for HPN was made between 2000 and 2006 British Artificial Nutrition Survey (BANS) data. Short bowel syndrome (SBS) remained the major reason for requiring HPN, although no information was given regarding the length of small bowel remaining or
the presence of the colon in continuity. One group in which numbers of HPN patients rose was those termed ‘other diagnoses’. This comprised a heterogeneous group of patients with mainly surgical complications. Cancer as the main diagnosis remained steady at 17% of new cases (Jones 2007).

1.5 Short bowel syndrome (SBS)

SBS usually results from repeated resection of small bowel strictures due to Crohn’s disease but can also result from extensive small bowel resection as a consequence of superior mesenteric artery/vein thrombosis or volvulus (Lal, Teubner et al. 2006; Irving 2000). However, a report from one IF unit demonstrated that the SBS in Crohn’s disease is more often a result of massive resection of inflamed and obstructed bowel secondary to peritonitis caused by anastomotic leakage than the pathology itself (Irving 2000).

Patients with less than 200cm of functional small bowel are generally said to have Short Bowel Syndrome. However, it is often more accurately defined by the proportion of bowel remaining and its functional capacity. Normal small bowel can vary in length between 300cm and 850cm and tends to be shorter in women. Congenital cases of SBS have been reported and many patients with a short bowel actually start off with a comparatively short length of intestine before resection. The degree of reliance on HPN depends on the absolute length and type of small bowel remaining. Children with less than 30cm of small intestine are unlikely to survive without long-term parenteral nutrition. Causes of SBS differ to those of the adult population. In neonates and infants, the most common causes are necrotising
enterocolitits, multiple small bowel atresias, aganglionosis and gastroschisis. Mid
gut volvulus is common in older children.

1.6 Small bowel physiology
The anatomy of the remaining bowel is important in determining the consequences of
a small bowel resection. Jejunal resections are better tolerated than ileal resections
due to the remaining ileal mucosa possessing tight intercellular junctions, which allow
concentration of its content. Transit times are also slower in the ileum, as a
consequence of the narrower diameter, allowing more time for absorption. Following
a small bowel resection, ileum is able to structurally and functionally adapt to boost
its function. Jejunum can only adapt if anastomosed to functioning colon. Patients
with an end jejunostomy show no form of adaptation. The three main types of patient
with short bowel include those with jejunal-colonic anastomosis, those with a
jejunostomy and those with jejunal-ileal anastomosis. All behave differently with
respect to their need for fluid and nutritional support, physiological changes following
surgery and gastric emptying (Nightingale 2001c).

1.7 Other reasons for HPN
Other patients have intact but non-functioning guts. Chronic motility disorders are
rare causes of intestinal failure. Total enterectomy gives symptomatic relief from
abdominal distension, vomiting and intermittent bacteraemia but results in type 3 IF,
with a lifelong dependence on parenteral nutrition.
1.8 Epidemiology

In Europe, Denmark is among the countries with the longest experience of HPN use in patients with intestinal failure. A five-year longitudinal study of HPN patients from 1996 to 2000 showed that 202 patients were treated during that time period, 34% had short bowel syndrome secondary to inflammatory bowel disease, 26% had cancer, 22% had surgical complications and 19% required parenteral nutrition for other reasons. At the end of 2000, Denmark had a HPN prevalence of 19.2 per million and an average annual incidence of five patients per million per year over the studied period. Data on numbers of HPN patients in the UK has been collected since the very first patients initiated on the treatment in St Marks Hospital, London and Hope Hospital, Salford in 1978. Since 1995, this has been logged centrally by the British Artificial Nutrition Survey (BANS), a constituent committee of the British Association of Parenteral and Enteral Nutrition (BAPEN) (Jones 2003). Each annual report has identified an increasing number of HPN patients. The most recent figures available, for 2006, suggest that numbers of new registrations remain static at about 100 per year (1.7/million population) whereas point (12/million) and period (12.5/million) prevalence continue to rise linearly. In 2006, there were 746 patients registered as receiving HPN in the UK. The number of centres providing treatment has decreased yet both point and period prevalence have risen, inferring new cases may be concentrating around larger centres (Jones 2007). From the most recent data available, it is clear that some centres are caring for very few patients. The two national IF centres have only 38% of new registrations since 2000. Concern exists as to whether these figures may have implications for quality of care of the patients in the longer term (BANS).
In Scotland, there were 11 new HPN registrations in 2006, a similar figure to previous years, however, as with the overall UK data, both point (85 patients) and period (16.7/million) prevalence have risen linearly since 2001 (Jones 2007).

The most recent European-wide data available for comparison gives point prevalences from 2002. (Table 1.1) (Wengler, Micklewright et al. 2006). The incidence and prevalence of HPN varies across Europe reflecting different organisational structures and treatment strategies (Staun, Pironi et al. 2009). Cancer is the predominant indication for HPN in the USA and Europe as a whole, but is the least common in the UK, Ireland and Denmark; in the UK, Crohn’s Disease is the commonest indication for HPN (Jones 2001).

**Table 1.1** European HPN registration point prevalence 2002

<table>
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<tr>
<th>Country</th>
<th>Point Prevalence in December 2002</th>
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<tr>
<td>France</td>
<td>186</td>
</tr>
<tr>
<td>Belgium</td>
<td>48</td>
</tr>
<tr>
<td>Italy</td>
<td>112</td>
</tr>
<tr>
<td>Poland</td>
<td>182</td>
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<tr>
<td>Denmark</td>
<td>132</td>
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<tr>
<td>Spain</td>
<td>18</td>
</tr>
<tr>
<td>Germany</td>
<td>41</td>
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In the UK, the commonest age range for new patients on HPN is 41-60 years; accounting for 50% of the new HPN patients (Elia, Russell et al. 2001). More recently, an upward trend in older patients (71-90 years) represent 14.1% of new
registrations. Point prevalence in this group is just under 7%; inferring survival rate in this group is not good (Jones 2003), however when the advanced age of these patients is considered, perhaps it is inappropriate to compare survival as an outcome.
1.9 Initiation of HPN

Historically, HPN was first attempted soon after in-patient parenteral feeding began in the late 1960s. The multi-bottle systems of feed were impractical, but by the mid-eighties ‘All-in-one’ solutions were widely used, allowing patients to return to normal activities including work and travel. Since then, the focus has turned to improving venous access, identifying and preventing complications, increasing awareness of the treatment, and developing support groups for HPN patients.

HPN aims to transfer the techniques used in hospital to the home and create conditions that allow patients to lead as active and fulfilling a life as possible. The Scottish Managed Clinical Network (MCN) for HPN set out criteria by which patients are selected for HPN therapy in Scotland.

- Patients considered for entry into a HPN programme should have documented IF which if untreated would lead to deteriorating nutritional and/or fluid status.
- Except in cases of short bowel syndrome with small bowel length of less than 50cm patients should have undergone a trial of enteral nutrition
- A clinician with an interest in and experience with IF, should assess patients with documented nutritional failure but no diagnosis.
- Training for HPN for up to a month requires the patient to be physically able to cope
- The ability of the patient to co-operate and preferences should be taken into account when assessing for HPN. An assessment should be made of the appropriateness of the domestic circumstances (Scottish Home Parenteral Nutrition Managed Clinical Network 2009)
• When HPN is given to patients with gastrointestinal obstruction secondary to cancer, patients must be unable to tolerate oral or enteral nutrition, willing to comply with HPN, have an expected survival of more than 3 months, an awareness of their diagnosis and prognosis and appropriate home support (Bozzetti, Cozzaglio et al. 2002).

There are a number of relative contra-indications for parenteral nutrition at home. These include patients with uncontrolled diabetes – especially those patients on insulin therapy who continue to experience significant fluctuations in blood glucose despite optimisation of insulin dosing and regimen, and patients with electrolyte abnormalities (of potassium, phosphate or magnesium for example) that are not easily corrected following replacement (Newton, DeLegge 2007). These comprise relative contra-indications, and parenteral nutrition at home may still be considered for these patients with appropriate supervision.

HPN is usually administered through a central vein catheter. It is normally given overnight as an all-in-one feed of approximately 3 litres, and on average administered five nights per week, with a wide range of between 2 and 7 nights. Some patients need saline and electrolytes bags instead of, or in addition to nutrition bags. This will depend on the length and type of bowel remaining and the presence or absence of a stoma. The catheter is situated so that its tip lies at the junction of the superior vena cava and right atrium. The most commonly used type has a subcutaneous cuff to prevent external migration and is capped off externally when not in use. A less frequently used catheter has an implantable port, which is cosmetically more desirable, but has a finite lifespan and cannot be repaired, necessitating surgical removal if problems occur.
A fridge is installed in the patient’s home solely for the purpose of storing the feedbags. The nutrient content varies according to the pathology and length of time on parenteral nutrition. Bags typically contain protein, glucose and lipid, electrolytes and vitamins.

The training and preparation of a patient for HPN can last between 3 weeks and 3 months and takes place concomitantly with treatment of the underlying disorder where possible. The aim of the education is to allow the patient to move from a passive dependence on professionals to an active participation and independence. Adequate and successful training will achieve a situation whereby the patient understands their illness, has confidence in managing their own HPN and has developed a good relationship with the nutrition team (Nightingale 2001a). In recent years, there has been a trend towards patients living in nursing homes, rather than in their own homes, with BANS data from 2000 documenting 5.8% of new registrations involving nursing home residents. This change has important implications for the additional training of nursing home staff in HPN administration (Elia, Stratton et al. 2002).

1.10 Provision of HPN

In the United Kingdom, patients suitable for HPN must be able to attend either a local nutrition team or a national IF centre. If neither is available, access to HPN treatment is denied. It is an important consideration whether the distances travelled by patients and their families for training, follow up and emergencies are manageable, especially with the increasing numbers of elderly patients commencing HPN therapy. It has
been documented that patients with a longer journey time are less inclined to present with symptoms and have an inevitably prolonged time to diagnosis and assessment of serious complications (Jones 2003).

In 1992 in the UK, the King’s fund recommended that all acute hospitals have a functioning nutrition support team (NST). In 1999, only 41% hospitals had followed this recommendation (Jones 2001). The most recent figures suggest that only 55% of adult centres contributing to the BANS report in 2003 had a NST (BANS). Despite this, it is a requirement that centres managing HPN patients have an NST, which comprises some or all of: nutrition nurse, physician, surgeon, dietician and pharmacist. In Europe, a different approach is followed. In France, there are only fourteen HPN centres and much of the follow up work is carried out in primary care. In Denmark, all patients are managed from a single expert centre. In England, the two IF units manage approximately 50% of the patients, whilst the other 50% are distributed amongst another 50 centres, many with only one or two patients intermittently (Jones 2001). In Scotland, a Managed Clinical Network has been set up to provide a facility whereby patients can be managed locally under national guidelines.

Outside of Europe, new Australasian guidelines have been published which by consensus opinion state similar criteria to other countries for commencing HPN, support the existence of a nutrition support team where possible for their patients and like Scotland, recognizes that some patients are living distant from centres with expertise in the care of patients on HPN and aim to provide support and
recommendations to clinicians caring for HPN patients in remote situation as well as in established centres of expertise (Gillanders, Angstmann et al. 2008).

American HPN patients are managed quite differently, mainly by the pharmaceutical home infusion staff, with individual physicians overseeing HPN in single patients or sometimes small groups of patients, and less than 20% of patients being managed by large medical institutions caring for upwards of 25 patients. This has been as a result of financial concerns regarding reimbursement to medical professionals for the time consuming nature of this work. The American Society for Parenteral and Enteral Nutrition (ASPEN), has published guidelines on monitoring patients which concur with the Scottish guidelines advocating multi professional management of patients. They also strongly emphasise the importance of patient participation in recognizing problems and ensuring appropriate monitoring (Siepler 2007).

The Scottish Home Parenteral Nutrition Managed Clinical Network (SHPNMCN)
The concept of MCNs began with the publication of The Acute Services Review of the National Health Service in Scotland in 1998. The aim of the network is to formalise previously informal arrangements to allow equity of access to optimal care via evidenced based procedures and a set of protocols. HPN treatment in Scotland was considered to be suitable for the formation of an MCN, as it is a treatment whereby it is beneficial to be treated in an experienced centre yet issues of equity of access and care exist due to geographical remoteness. The HPN MCN was established in 2000 and is funded by the National Services Division of the Common Services Agency on behalf of the Scottish Executive. Members are multiprofessional in origin, spanning all the expertise necessary for the safe provision of HPN and in
addition there is patient representation. In contrast to the UK as a whole, the HPN MCN is confident of its numbers of HPN patients, as communication throughout the network is excellent and the coordinator is in close contact with all nutrition teams. When the MCN was formed, locally prepared protocols were reviewed and consensus opinion used to agree MCN national protocols that are followed locally by each hospital. A quality assurance framework is in place to ensure standards and safety of HPN delivery. The Clinical Standards Board for Scotland, now known as Quality Improvement Scotland, has provided approval. A computer database collects data prospectively from all HPN sites in Scotland, allowing both national audits and the facility for research across a whole patient population. The resource of an MCN can increase adherence to protocols, which has been shown to lessen complication rates (BAXTER, MCKEE 2003; Santarpia, Pasanisi et al. 2002). Additionally it provides a large amount of experience, a support network and an ongoing education, which in previous studies both in the UK and abroad, have been linked to complication rate reduction and an improved outcome (BAXTER, MCKEE 2003; Smith, Curtas et al. 2002b; Reimund, Arondel et al. 2002; Johnston, Richards et al. 1994). The logistics of delivery and the provision of equipment has now become standardised across Scotland due to National Procurement securing a contract with a single pharmaceutical company to supply and deliver all necessary equipment and feed.

1.11 Cost effectiveness of HPN

HPN must compete for limited NHS resources. When the expense of HPN is considered, it is surprising that, to date, more studies have not addressed the economic cost effectiveness of this treatment. A cost-analysis by Richards et al 1997, stated that the first year cost of HPN per patient was £43 000. The marginal cost per QALY
was £63 000. The annual cost of hospital total parenteral nutrition (TPN) per patient was found to be £93 000, giving a 65% saving in financial terms alone by facilitating a HPN service and discharging patients from hospital. An older study by Wateska et al supports this finding, noting a cost reduction of 73% for HPN. Subsequent years of HPN treatment were found to cost £36 000 per annum (Richards, Deeks et al. 1997). Periodic review of patients was recommended by Baptista et al to ensure prescriptions, equipment and patient behaviours were regularly assessed to optimise costs. More specifically, even less is known regarding cost effectiveness in subgroups of HPN patients such as those with malignant disease or AIDS. If these patients were included the cost per QALY would increase dramatically. Other questions raised by Richards et al were whether there was any financial benefit to different organisational models, for instance small or large HPN units. This was addressed by Curtas et al who recognised the cost of a nutrition support team, the inference being that the greater the number of patients followed by a team, the lower the cost per patient (Curtas, Hariri et al. 1996).

In Scotland, the issue of cost has been addressed recently by the MCN. A national contract has been awarded to provide HPN to all patients across the country. Regular reports on key performance indicators are provided and since the contract was implemented in 2007 approximately £725 000 has been saved between new and existing HPN patients.

**1.12 Outcome of HPN therapy**
It is established that HPN patients’ outcome is the product of factors such as underlying disease, general clinical condition, level of support by professionals and family, education and facilities (Bozzetti 2003).

Data collected by the British Artificial Nutrition Survey demonstrate 92% overall one year survival of UK patients receiving HPN (Jones 2003). In comparison, recent retrospective studies from North America and Europe report five-year survival of patients receiving HPN to be within the range of 60% to 78% (Messing, Crenn et al. 1999; Vantini, Benini et al. 2004; Jeppesen, Staun et al. 1998; Scolapio, Fleming et al. 1999; Lloyd, Vega et al. 2006). The majority of these studies were carried out in centres of excellence. Factors found to be associated with a poorer prognosis include small bowel length <50cm, age at initiation of HPN and the underlying diagnosis (Vantini, Benini et al. 2004; Scolapio, Fleming et al. 1999). Patients less than 40 years old and those with inflammatory bowel disease have been found to have the best prognosis (Pironi, Paganelli et al. 2003).

Parenteral nutrition dependence is a second outcome examined in cases of short bowel syndrome. The syndrome can be associated with either transient or permanent intestinal failure. The probability of PN dependence is associated with length of small bowel remnant and type of anastomosis present. Parenteral nutrition dependence was found to be 49% at two years and 45% at five years. Intestinal transplantation is a viable alternative to HPN for patients with irreversible intestinal failure. This is as a result of both improved patient and graft survival. The importance of determining long term PN dependence and survival statistics in the SBS group of patients is to facilitate the decision of when and if to consider intestinal
transplantation. It is useful and valuable therefore, to identify patients with particularly poor prognoses on HPN and whether this is as a result of their parenteral nutrition or their underlying disease process (Lloyd, Vega et al. 2006).

Most HPN studies reporting outcome data have generally had either single centre experience or experience of tertiary referral centres where large numbers of highly selected intestinal failure patients are treated. Patients in UK tertiary centres are broadly from two subpopulations, those who are well enough to travel the distances to the Intestinal Failure units and those who are highly complex and sent from around the UK to be managed in expert centres. Of interest would be a study whereby all comers to the treatment are included and their data analysed. In Scotland, the Managed Clinical Network provides HPN locally throughout Scotland and consequently a study of Scotland’s HPN patients provides the chance to review a complete population of patients. As a result of the network and the consequent availability of HPN across this wide geographical area, we are provided with this diverse demographic to consider.

1.13 Intestinal transplantation as an alternative

Intestinal transplantation has shown huge advancement over the past decade, in both volume of operations performed and also in outcome. The majority of operations are carried out in the United States where the number of patients listed has increased steadily from 87 in 1997 to 236 in 2006. The median time to transplant is one of the longest of any solid organ, with a current average of 261 days and mortality remains high whilst on the waiting list, more than double all other solid organs (Freeman, Steffick et al. 2008). Expected survival following intestinal transplantation remains
lower than expected survival on HPN, making HPN the treatment of choice for irreversible chronic intestinal failure, on both safety and efficacy grounds. As such, the main indication for intestinal transplant is failure of HPN due to life threatening complications or lack of venous access; another is a locally invasive tumour of the abdomen. Other than these, there are no absolute indications for considering intestinal transplant; however some patients are simply unwilling to contemplate life-long intravenous nutrition (Pironi, Paganelli et al. 2003). In 2005, a study in Europe was undertaken to examine the need for intestinal transplant, based on American criteria. It found that the rate and indications for candidacy differed between adults and children, with paediatric rates twice as high as adult ones. Adult indications were mainly related to failure of HPN whereas a high risk of death related to the underlying condition (pre-emptive intestinal transplantation) was most common in the paediatric population. It also concluded that, in general, doctors had a reserved attitude towards intestinal transplantation and that this may be resulting in late referrals to the waiting list. There was huge variation between countries in timing of referral, due mainly to the lack of guidelines (Pironi, Hebuterne et al. 2006). In America, insurance agencies approve payment for intestinal transplant when life-threatening HPN complications occur. The American Society of Transplantation considers paediatric indications to be similar but additionally include children with a high risk of death or very poor quality of life related to the underlying IF. The outcome following intestinal transplantation is improving, and although still behind other solid organ transplants, the major development in immunosuppression in the nineties has seen the one-year survival improve to above 50% (Middleton, Jamieson 2005; Sudan 2007). In the UK published literature, only 14 adult transplantations have been undertaken over the last 15 years, despite the numbers of patients receiving HPN increasing steadily
A poster at the British Association of Parenteral and Enteral Nutrition conference in October 2010 reported the results of a single UK centre over the last three years. Thirteen transplants were performed over the last three years with an overall 92% survival, including one death due to occult malignancy (Wiles, Butler et al. 2010).

1.14 Complications of HPN

HPN shares all the complications of parenteral nutrition, yet additionally, it has its own specific problems related to the long term nature and complexities of the treatment. These problems can lessen the success of HPN and can also adversely affect quality of life and influence prognosis. At their most serious, HPN related complications can be fatal (Pennington 1991). The patient also has the underlying disease to contend with, and the natural progression of this can further complicate the satisfactory delivery of HPN (Jones 2001). HPN related complications fall into categories including catheter related sepsis, venous thrombosis, mechanical and metabolic problems.

1.15 Macronutrients

The macronutrients protein, carbohydrate and lipid are substrates for anabolism and energy production. Their effects are dependent on both their relative concentrations and the recipient individual. If the amounts provided are below that of the Recommended Daily Allowances (RDA), tissues are broken down to provide the missing energy. If excess macronutrients are supplied, they are stored as glycogen or fat. In the healthy subject, the provision of macronutrients ensures the maintenance of lean body mass. In contrast, sick patients are in a catabolic state and nutrients
prevent loss of further lean body mass in addition to repairing wounds and aiding healing. Nutritional requirements themselves do not differ in these groups of patients but quantities and proportions of amino acids, carbohydrates and lipids may vary. Requirements are determined by nutritional status assessment and taking into account the specific diagnosis of the patient, which can imply specific deficiencies.

1.16 Micronutrients

Micronutrients can be difficult to measure, and as such knowledge of requirements is minimal, especially in disease states, but they are known to have two main functions. Firstly, micronutrients have a key role in intermediary metabolism as cofactors or coenzymes in enzyme-catalysed reactions. Secondly, they are part of the free radical scavenging system, whereby they protect tissues from the reactive oxygen species generated by the metabolic response to disease. Increasing degrees of micronutrient deficiency have a progressive effect on patients before a clinical deficiency syndrome is reached and diagnosed. Depletion initially leads to reduced body content, followed by a reduction in both metabolite synthesis and cellular metabolism through the lack of vitamin-dependent enzymes and hormones (Shenkin 2001).

Most patients who require HPN will have been in hospital for a substantial period and will have been stabilized on an appropriate micronutrient regimen for their requirements. Some patients may still have issues with tissue mass to regain and stoma losses to compensate for. The micronutrients in HPN preparations are based on the nutritional requirements of patients who are catabolic or already malnourished and therefore are designed to provide more than the Reference Nutrient Intake,
delivered intravenously they should more than meet requirements for most individuals.

It is still possible for patients receiving HPN to develop micronutrient deficiencies for several reasons. Sometimes micronutrients are actively withheld from patients. This is seen in cholestasis, when manganese and copper, which both undergo biliary excretion, are withheld to prevent a toxic accumulation of either nutrient. Patients who consume some oral diet are assumed to gain a proportion of their micronutrients this way; this is entirely dependent on the diet consumed and its nutritional value. Additionally, there is a potential risk of nutrient degradation within the HPN mixture or chemical changes for nutrients such as ascorbic acid, thiamine, riboflavin, zinc and copper (Bozzetti, Staun et al. 2006).

Approximately thirty percent of HPN patients may have a micronutrient deficiency but this rarely causes clinical consequence. The most common deficiency is of iron, which resolves with supplementation (Forbes, Forbes 1997). A study by Forbes and Forbes (1997) found concomitant folate deficiency in two iron-deficient patients and illustrates the importance of considering the presence of other deficiencies when anaemia is diagnosed. The same study investigated the incidence and nature of clinical micronutrient abnormalities within their HPN population. Micronutrient assays were performed and all patients studied had at least one micronutrient level outside the reference range. All but one of the 32 patients had an abnormally raised manganese level. On clinical review, it was not possible to determine the individuals with these abnormalities. The study concluded that abnormalities of micronutrient
levels are common in HPN patients but serious sequelae are unusual (Forbes, Forbes 1997).

Micronutrient deficiencies with known consequences include cardiomyopathy from severe selenium deficiency and neuropathy with too little vitamin E. Selenium doses in HPN are believed to be sufficient for maintaining selenium status but are inadequate for replacing depleted stores or for patients with an increased demand (Malone, Shenkin et al. 1989). A case study of zinc deficiency highlights the need for addition of this essential component to HPN. A vesicular pustular rash was noted and early ulcerations were present on the fingers of a patient receiving long term parenteral nutrition without zinc addition. Serum trace elements confirmed zinc deficiency and the dermatological condition resolved with intensive zinc supplementation (Jones, Lamb et al. 2007). Copper deficiency in patients on TPN usually manifests clinically after several months as haematological abnormalities e.g. leukopaenia, neutropenia and anaemia (Fleming 1989).

For most micronutrients, the safety margin between adequate provision and toxic dose is large and there is minimal risk of excessive provision. However, HPN can occasionally result in an excess of micronutrients due to the non-physiological delivery of the nutrition, which bypasses the regulatory role of the liver and makes them 100% bioavailable. Metals can accumulate in the tissues in this way. Over 50% of HPN patients may have elevated blood levels of manganese and over the years there have been multiple reports of excess manganese accumulating in the brain of HPN patients, presenting with Parkinsonian symptoms. This is thought to be either secondary to excess provision or inadequate biliary excretion. Cholestasis is
likely to be less important than excess provision (Wardle, Forbes et al. 1999), although patients with chronic inflammation are more likely to develop hypermanganesaemia, with abnormal biochemical LFTs (Reimund, Dietemann et al. 2000). Manganese deficiency in humans is rare and growing evidence of the frequency of manganese toxicity suggests that parenteral supplementation may be too high. A combination of PN contamination with manganese and dietary sources in those patients managing some oral diet may be contributory, and even be sufficient to withdraw manganese from trace element mixtures (Hardy, Gillanders et al. 2008). Chromium has also been reported in high levels, and this seems to be through a mixture of intentional provision to avoid a deficiency state, and the contamination of parenteral nutrition solutions with chromium. The consequences of chromium excess are not clear (Bozzetti, Staun et al. 2006). A third trace element to accumulate is copper. This is believed to be due to the disruption of the enterohepatic circulation and cholestastic liver disease and is independent of duration of HPN therapy (Blaszyk, Wild et al. 2005).

Metabolic bone disease (MBD) is a complex and common problem in patients receiving HPN. It can be a major cause of morbidity and because of this patients should be monitored regularly for both osteomalacia and osteoporosis. Equally it can be asymptomatic and the diagnosis is at times incidental. Risk factors for MBD include the underlying disease and its consequent treatments, such as radical surgery and long-term corticosteroids through renal calcium excretion, prolonged inactivity, and smoking. Patients can begin their HPN with pre-existing calcium and magnesium deficiencies and vitamin D-deficient osteomalacia. Symptoms of this, including periarticular bone pain and tenderness, often worsen as HPN therapy is
established, due to weight gain and growth; this is known as the ‘paradox of rickets’ (Jones 2001). In 2000, an Italian study compared HPN patients of less than four months with patients of greater than twelve months duration and showed that initially bone turnover increased. After six months this turnover returned to normal but bone formation was increased, this also settled to low or normal rates after one year of treatment (Pironi, Labate et al. 2002). However, in contrast, a Canadian group led by Jeejeebhoy concluded that the bony pains are due to vitamin D-induced osteomalacia which can recover when vitamin D is withheld from HPN bags (Jeejeebhoy 1998). Osteoporosis is a debilitating problem found with long term HPN. These patients have an excessive urinary excretion of calcium and phosphorus, but normal serum biochemistry including vitamin D (Pennington 1991). Magnesium deficiency inhibits parathyroid hormone secretion, the consequence of which is decreased calcium absorption from the gut. Correction of magnesium, calcium and phosphorus levels help to minimise osteoporotic changes, light weight-bearing exercise is encouraged and either regular oral, or annual intravenous, bisphosphonates (which circumvent the variable bioavailability due to short gut syndrome in HPN patients) are frequently used (Staun, Pironi et al 2009). In addition, recombinant parathyroid hormone may be used in the treatment of MBD in HPN patients. The role of vitamin D in bone disease remains inconclusive (Btaiche, Khalidi 2004). All patients should have bone densitometry performed (DEXA scanning) when entering an HPN programme and thereafter yearly or when metabolic bone disease is suspected (Buchman, Moukarzel 2000).

1.17 Metabolic complications of HPN
Many diseases have both qualitatively and quantitatively abnormal requirements and in some patients, disease states can render non-essential nutrients essential due to a compromised biosynthetic capacity. Additionally, parenteral nutrition solutions are anabolic in nature, and in the acute setting, refeeding a malnourished patient can precipitate a deficiency state (Thorell, Nordenstrom 2001). The most important nutrient deficiencies are hypoglycaemia and hypophosphataemia. Rebound hypoglycaemia can occur due to high insulin levels if feed is stopped abruptly. Patients may be taught to reduce the rate of infusion gradually to prevent this problem. An extracellular hypophosphataemia is caused by the intracellular influx of phosphate in response to carbohydrate load and insulin release (Thorell, Nordenstrom 2001). Severe hypophosphataemia results in a decrease in function of multiple systems including respiratory, cardiac and neurological. The addition of phosphate to the feed prevents this rare but serious complication of short term parenteral nutrition.

1.18 Hepatobiliary complications

Patients receiving home parenteral nutrition are at risk of developing hepatobiliary complications ranging from mildly deranged liver function tests (LFTs) to life threatening end stage liver disease. This can present late and in this situation is often irreversible, the only possibility of recovery through combined liver and small bowel transplantation. Data from the International Transplant Registry (2001) suggests that 55% of patients with HPN-related liver disease require a combined liver/intestinal transplant at the time of referral. The incidence of liver complications increases with duration of parenteral nutrition (Henkel, Buchman 2006). Cavicchi et al showed this by demonstrating that the prevalence of chronic cholestasis (two of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase raised to 1.5 times
their normal level for greater than six months) increases with duration of HPN, 55% at 2 years, 64% at 4 years and 72% at 6 years (Cavicchi, Beau et al. 2000). Many studies have examined the aetiology of HPN-associated liver dysfunction and no single factor has been identified. Liver disease is more common in children and in short bowel patients, remnant small bowel<50cms, although this is thought possibly to be directly related to the consequent provision of HPN for long durations (Lloyd, Zabron et al. 2008), small bowel bacterial overgrowth, bowel rest and disruption of bile acid (Chan, McCowen et al. 1999; Btaiche, Khalidi 2004). Excessive dextrose or total calories, proportionally excessive calories derived from lipids, choline deficiency, essential fatty acid deficiency and hepatotoxins have all been implicated (Chan, McCowen et al. 1999). Current research is focussed on hepatic transulphuration pathways as a contributor to HPN-related liver disease. Methionine is the only sulphur-containing amino acid in HPN due to its solubility. Intravenous delivery avoids the physiological portal system and methionine is transaminated to mecaptans rather than normal downstream products important in mobilising fat and synthesising lipid membranes for bile secretion (Howard, Ashley 2003). Other reasons for deranged liver function include pre-existing illness such as Crohn’s disease and multiple episodes of sepsis. Crohn’s may lead to abnormal liver function via a number of routes. Primary sclerosing cholangitis – presenting typically with an elevation in alkaline phosphatase or gamme GT – may affect 5% of patients with Crohn’s disease. Cyclical infusion of HPN has been found to reduce the incidence of liver-related complications when compared with continuous infusions. Medical treatment options for HPN-related liver disease include encouraging oral intake, limiting parenteral lipid calories, treatment of bacterial overgrowth with prokinetic agents and antibiotics, oral or parenteral provision of carnitine and choline and the
prescription of ursodeoxycholic acid, which is thought to work by correcting the bile salts. In the absence of oral or enteral nutrition, about 25% of HPN patients develop cholelithiasis secondary to the lack of cholecystokinin release and consequent decreased gallbladder contractility. The bile accumulation leads to the formation of cholesterol stones in the gallbladder and the development of a biliary sludge. Most surgeons do not remove the gallbladder prophylactically at the time of the initial surgery and patients undergo cholecystectomy only if they develop problematic gallstones (Howard, Ashley 2003).

1.19 Catheter related complications of HPN

In a systematic review of HPN in 1997, Richards et al reported that catheter sepsis occurred at a rate of 0.34 episodes per catheter year, which equates to one episode every 2-3 years. Similarly, catheter occlusion and central venous thrombosis were reported to have incidences of 0.071 and 0.027 episodes per year respectively. More common were problems with fluid and electrolyte imbalance at between 0.12 and 0.61 episodes per year (Richards, Deeks et al. 1997). A study at the Mayo Clinic reported that of their 225 HPN patients over the past 20 years, 45% had needed no further hospitalisation following their commencement on therapy, a further 48% required between 1 and 6 readmissions. The most common reason for admission was catheter related infection, followed by electrolyte disturbance, liver disease and metabolic bone disease (Scolapio, Fleming et al. 1999).

Fever can have many causes in a patient receiving HPN. One important differential to be considered and excluded is that of catheter related sepsis. Symptoms and signs are often sub clinical and subtle and so a high degree of suspicion is necessary. On
average, this occurs every 2-3 years in adults and with twice this frequency in children. Patients receiving HPN for prolonged periods benefit from a decreased rate of catheter infection (Buchman, Moukarzel et al. 1994). Catheter related infection is the most common reason for readmission to hospital so prevention is very important both for the patient and for the cost effectiveness of the treatment. The most valuable tool for this is patient education and training by an experienced HPN nurse, and this appears to be most beneficial if tailored to the individual patient, taking into account intellectual and manual skill level (Reimund, Arondel et al. 2002). The preventative role of careful training is further supported by a French study which found that patients given detailed written information together with several theory and practical sessions and often a monthly follow up did significantly better with regard to catheter infection (8%) than patients given more brief instruction and no follow up (21%) (Santarpia, Pasanisi et al. 2002). Also significant is the experience of the hospital managing the HPN. There is a documented inverse correlation between the incidence of catheter related infection and a teams’ experience level with HPN (Johnston, Richards et al. 1994, Mughal, Irving 1986) and even within a team, the number and frequency of catheter infection can be shown to decrease as the team gains experience (Reimund, Arondel et al. 2002).

Patients with motor disorders have increased catheter infection rates, presumably through a high rate of bacterial translocation (Reimund, Arondel et al. 2002). It is possible that this is also the case in short bowel syndrome where mucosal integrity is altered by the physiological adaptation (de Burgoa, Seidner et al. 2006). There is a trend towards higher rates of catheter related infection in patients with stomas or fistulae. A study by O’Keefe et al of his HPN patients concluded that a jejunostomy
was a risk factor for catheter related infection, speculating that the mechanism of this is most likely to be touch contamination (O'Keefe, Burnes et al. 1994).

Conditions surrounding the placement of the intravenous catheters can also have a significant effect on whether subsequent infections develop. Biofilms form as a matter of course on both the external and internal catheter surfaces and it is the dispersal and dissemination of the biofilm bacteria into the bloodstream which causes catheter-related blood stream infections (CRBSI). Bacteria are impacted on the tip of the needle as it traverses the epidermis during insertion. Effective skin cleansing prior to insertion of the catheter can fundamentally and significantly affect rates of extraluminal CRBSI. In addition, chlorhexidine gluconate impregnated dressings can significantly reduce CRBSI rate when compared to transparent polyurethane film dressings. Intraluminal infections are a major source of CRBSI in long term catheters and can be minimised by a combination of hand hygiene, access site disinfection and antimicrobial flush solutions after use (Ryder 2006). Diagnosis of CRBSI is usually by positive blood cultures obtained through the catheter as well as peripherally. A more precise and advanced diagnostic technique is that of obtaining a quantitative catheter blood culture value whereby the central culture is five-fold greater than the value obtained peripherally. The original management of CRBSI was to remove the infected line and treat systemically with antibiotics. As central venous access is a precious commodity in HPN patients, treatment has progressed to use an antibiotic lock within the catheter wherever possible to prevent loss of the catheter. There are occasion when infections with specific bacteria render line preservation potentially harmful, with the possibility of metastatic infection (particularly in the case of
Staphylococcal infection). In these circumstances, line removal is the preferable course of action.

Catheter occlusion can occur as a result of fibrin, lipid or amorphous debris build up on the intraluminal surface of the catheter. When blood is left within the lumen of the catheter, a thrombotic occlusion may also develop. These complications are minimised by two interventions, catheter flushing and the use of antireflux needleless connectors and valves (Ryder 2006). A positive correlation between thrombotic occlusion and catheter infection has been described (de Burgoa, Seidner et al. 2006).

Catheter fracture is a further serious complication which all HPN patients are warned of prior to discharge from hospital. There is a risk of air embolism, haemorrhage or infection when the integrity of the catheter is lost (Pennington 1991). Patients are taught to clamp the line before seeking help from health care professionals. The problem usually occurs close to the hub of the catheter where it is clamped and as such, most patients now use an extension tube which can be changed regularly to avoid wearing. Increased incidence of fracture is suggested with the practice of intraluminal brushing used to unblock catheters and aid precise diagnosis of catheter related infection (Jones 2001).

HPN patients are at risk of central venous thrombosis (CVT) for several reasons including suboptimal catheter positioning, underlying condition and prothrombotic HPN components. It is well established that catheters placed in the superior vena cava (SVC) instead of the right atrium are at an increased risk of thrombosis (Pennington 1991). Underlying conditions predisposing to CVT include Crohn’s
disease, due to the platelet abnormalities present, the prothrombotic tendencies of neoplastic diseases (Pennington 1991) and the primary coagulation disorder in mesenteric infarction. (Messing, Hebuterne et al. 2001). With respect to Crohn’s disease, platelet abnormalities include thrombocythaemia and hypersensitivity to agonists including epinephrine, collagen and adenosine diphosphate (Matsumoto 2006). Further to this, malnutrition presents additional risks of essential fatty acid deficiency and hyperhomocysteinaemia for all HPN patients (Compher, Kinosian et al. 2001). Following the establishment of a relationship between glucose concentration and CVT, a study by Pennington et al found that modifying the glucose concentration in HPN bags led to a significant fall in CVT rates over subsequent years (Johnston, Richards et al. 1994).

1.20 Paediatric HPN

The natural history of intestinal failure in children is variable. Most children with acute IF, usually secondary to gastrointestinal infection, recover with appropriate treatment. Paediatric cases of short bowel syndrome leading to chronic intestinal failure are often secondary to surgery for congenital anomalies or necrotizing enterocolitis. They generally retain their colon and adapt gradually over several years, enabling them eventually to cease HPN. In addition, there are children with severe chronic intestinal failure, who without long term parenteral nutrition or, when possible, small bowel transplantation would not survive. Paediatric diagnoses leading to lifelong HPN dependence include mucosal diseases such as congenital microvillus atrophy and neuromuscular disorders for example chronic intestinal pseudo obstruction (Milla 2001). Ethical dilemmas are addressed and decisions made after careful discussion with parents and professionals.
To formulate paediatric feeds, a regimen is calculated per kilogram body weight per day. In cases of long term growth failure, caloric intake is related to expected rather than actual weight. Complications with paediatric parenteral nutrition are dominated by catheter problems, as in the adult patient. Catheter sepsis should be suspected when infection is queried but no source is known. It is more common in children than in adult patients and may be associated with non-specific symptoms and signs including fever, unstable blood sugar, diarrhoea and vomiting. Causative agents may differ, with Gram negative isolates as common as Gram positive ones. Psychologically, failure to provide parenterally fed infants with oral nutrition or stimulation can lead to feeding difficulties or food rejection at a later stage. This is minimised by involving speech and language therapists early and offering food or ‘dummies’ where appropriate. Other aspects to consider and limit are long periods of isolation during feeding and immobility due to pumps and other equipment (Puntis 2001).

1.21 Quality of life after starting HPN

Quality of life (QoL) in HPN patients depends upon good technical skills, leading to fewer line infections and subsequent hospital admissions. In 2005, Persoon et al, using questionnaires and interviews, found that most patients were attributing psychological symptoms to underlying disease processes rather than HPN treatment (Persoon, Huisman-de Waal et al. 2005). Baxter et al also reviewed QoL findings of previous studies and concluded that separation of disease process and HPN technology issues would be required to better evaluate QoL and a disease specific HPN QOL would be ideal. A later paper by Huisman-de Waal et al reviewed
multiple QoL studies in HPN patients and concluded that overall, HPN patients experience a moderate to good QoL, but that many suffer fatigue and depression, somatising psychological symptoms (Huisman-de Waal, Schoonhoven et al. 2007). Smith et al found that the patients supported by an organisation had a mean score indicating no (or mild) depression, while the mean scores for the patients who were not supported indicated moderate depression (Smith, Curtas et al. 2002a). Anxiety was also a feature in many studies, common fears mentioned included the fear of death and of liver failure. Worthy of note, levels of anxiety were found to be higher in HPN patients than in patients having undergone small bowel transplantation (DiMartini, Rovera et al. 1998). An important indicator in the assessment of outcome. Social aspects of life were also found to be compromised by HPN. Activities such as child care, shopping and sports were areas where patients had to make adaptations. Going on holiday was problematic, and the logistical arrangements demanding. However, the longer the patients were on HPN, the less the effect on travel (Huisman-de Waal, Schoonhoven et al. 2007; Chambers, Powell-Tuck 2007).

1.22 The Patient Perspective

Since 1993, surveys have questioned and utilised patient opinion on all aspects of HPN. This has helped appreciate and understand issues important to patients concerning this highly specialised treatment.

The journey starts with a patient being told by medical staff that they would benefit from commencing parenteral nutrition. After concerns regarding previous treatment failures and future challenges are discussed, the patient begins the process of
accepting the feeding tube and learning to use the equipment. This takes a variable amount of time and a huge amount of support from specialist nursing staff and dieticians. Once home, the patient and family must adjust and settle into a routine that suits. There is telephone support available and follow up with nutrition support teams regularly. Deliveries of feed and equipment are made regularly and feed must be refrigerated at a constant temperature until used. Some patients manage to return to work and by arrangement travel on holiday to destinations where bags of feed can be delivered. Parenteral nutrition bags have been delivered all over the world. Support groups such as PINNT (Patients on Intravenous and Nasogastric Nutrition Therapy) are established and provide a network of support and understanding from patients undergoing similar challenges.
Chapter 2

Home Parenteral Nutrition in Scotland: Frequency of Monitoring, Adequacy of Review and Consequence for Complication Rates

2.1 Introduction

Parenteral nutrition can improve the recovery and survival of patients who would otherwise suffer from malnutrition. However, it can itself be associated with adverse effects of mechanical, septic or metabolic origin (Nordenstrom 2001). For HPN to be effective it is essential to ensure that the nutrients provided are adequate and are being utilized effectively. Regular monitoring of HPN patients serves several purposes, including the assessment of general wellbeing, identifying and helping with possible problems in feeding technique and potential complications - as well as the assessment of nutritional intake and monitoring weight, laboratory data and other outcome factors. By the time a patient is discharged from hospital he or she is likely to be more metabolically stable and monitoring does not need to be carried out as frequently as whilst an in-patient. Few studies have been conducted to investigate the diagnostic efficacy or cost-effectiveness of monitoring patients receiving any form of nutritional support, and even less information is specific to HPN patients. The NICE guideline recommends review by home care specialists and by experienced hospital teams, initially at least weekly. Long term, it is recommended that review be undertaken three to six monthly at a specialist hospital clinic (National Collaborating Centre for Acute Care. Commissioned by the National Institute for Clinical Excellence 2006).

Newly published ESPEN (European Society of Parenteral and Enteral Nutrition) guidelines on Parenteral Nutrition (Staun, Pironi et al. 2009) advise the monitoring of
biochemistry and anthropometry at all visits; vitamins and trace elements at six monthly intervals and investigations for metabolic bone disease annually. ASPEN (American Society for Parenteral and Enteral Nutrition) (Siepler 2007) recommendations have some similarities to ESPEN such as annual bone densitometry. However, they also recommend slightly different intervals for monitoring other elements, with monthly to quarterly biochemistry and liver function tests, quarterly iron and folate, quarterly to annual trace elements and annual vitamins. ASPEN also documents a requirement for annual quality of life assessments, the need for which is discussed in the European guidelines, without formally suggesting an interval for regular Quality of Life (QOL) measurement in their Summary of Statements.

In Scotland, a patient receiving home parenteral nutrition benefits from the HPN Managed Clinical Network (MCN), which sets standards, approves protocols, conducts audit, measures outcomes and encourages multi professional care. Due to the lack of published studies, the Scottish HPN MCN guidance, like that of NICE, is based on expert opinion rather than higher levels of evidence, and recommends that initially the patient should be observed closely and the first clinic visit should be within 1-2 weeks of discharge from hospital. Thereafter, it is recommended that they are seen every three months as an out-patient (Baxter, McKee et al. 2007). The HPN MCN guidelines state that the patients’ weight, haemoglobin, indices of inflammation such as white cell count and C-reactive protein (CRP), renal function, liver function, calcium and magnesium, micronutrients, vitamins and anthropometry should ideally be measured at each HPN review. Anthropometry should include triceps skin fold thickness (TSF), mid upper arm circumference (MUC) and mid arm circumference (MAC).
Scottish, ESPEN and ASPEN guidelines are very similar with respect to most aspects of HPN monitoring, with the exception of anthropometry which is not mentioned in the American guidelines and their obligatory annual QOL surveys for which they use a generic quality of life assessment tool. QOL measurement is not yet formalised in European guidelines, but a specific tool for measurement in HPN patients is being developed. All three guidelines are based on experience as evidence based guidelines are not yet available.

The aim of this study was to assess the degree to which this guidance on HPN monitoring by the Scottish HPN MCN is adhered to, and to determine whether any relationship exists between frequency of review and complication rate in HPN patients.
2.2 Materials and Methods

All patients receiving HPN funded by the NHS (National Health Service) in Scotland are known to the MCN through both direct contact with the Network Manager and the National Contract for Parenteral Nutrition Provision in Scotland. Patients were included in this study if they were on HPN for at least three consecutive months during 2006. A figure of one hundred days was taken as the recommended frequency against which all patient reviews were compared. Data was collected primarily from the purpose-built *Microsoft Access* database, which is completed by nutrition teams at all HPN MCN centres for each patient and each visit. All patients receiving HPN in Scotland are entered prospectively on to the database, which holds patient data since the creation of the MCN in 2000. Recorded information includes patient demographics, catheter and feed details, blood results, clinic review findings, complications and termination of treatment information. Missing or queried data was resolved through personal visits to the hospitals concerned and review of patient notes or by contacting the local nutrition teams. Patients were placed into three groups, dictated by how often their inter-review interval met the one hundred day guideline. Within the three groups, median time on HPN treatment was calculated to assess any correlation between regularity of review and duration of home parenteral nutrition. Complications were divided into HPN and disease related categories. HPN complications included central venous line problems and metabolic concerns related to intravenous feeding. Disease related complications covered issues secondary to the disease process as well as pre and post surgical problems. The incidence of complications in each group was compared using a chi-squared test.
2.3 Ethics

This study was discussed with the Glasgow Royal Infirmary Ethics Committee who deemed that the data was already being collected and stored with patient consent, prior to this study. In view of this, no ethics committee approval was necessary. All patients involved in this study are made aware of the ongoing collection of data and audit at the start of their treatment.
2.4 Results

In 2006 a total of 53 patients received HPN in Scotland for three or more consecutive months. The patients attended 141 HPN clinic appointments, an average of 2.6 clinics per patient within the selected time frame. There was a wide variation in the number of patients at different centres - between 1 and 20 for the studied year. Numbers of clinic appointments per hospital therefore also varied greatly between 2 and 49 within 2006. Patient demographics, range of diseases and HPN indications are found in Table 2.1. Data was collected from seven of the nine nutrition hospitals responsible for overseeing HPN treatment. Two Scottish hospitals had no patients meeting the inclusion criteria during the period examined and are therefore not represented in this study.

The frequency of monitoring was considered in two ways. Firstly, did patients’ review intervals meet the set standard? When the database was examined, three broad groups of patients resulted. Approximately one third fell into each group, with 30% meeting the standard on all occasions, Group A, 36% meeting the standard on some of their visits during the studied year, Group B, and 34% never being reviewed within the set standard throughout 2006, Group C. The range of interval length between reviews was considerable, with twenty-seven of the appointments (19%) more than two hundred days following the previous review. However, there were twenty-five patients (45%) who breached the standard on just one occasion throughout the study period, with all other appointments meeting the target.

Secondly, individual clinic reviews rather than patients were considered as to their frequency of monitoring. Eighty-five clinic reviews (60%) met the standard of
review frequency. Fifty six clinic outpatient clinic reviews (40%) were outwith the set standard. The patients who were not seen within 100 days on every occasion were distributed between all seven hospitals. Examining these clinic reviews by centre, the range of outpatient appointments meeting the target at individual centres varies between 0% and 77% however these results correspond to small hospitals with only one or two patients and two or three clinic appointments each. One hospital never met the standard but this reflected the clinic reviews of just one patient. The majority of hospitals had more patients and conducted between 40% and 67% of scheduled reviews within the guideline of 100 days. Three patients were unable to attend scheduled clinic appointments and consequently were reviewed later than planned, despite the efforts of the local nutritional teams to provide alternative dates to accommodate them. A further eight patients had blood taken and tested but no evidence of formal review.

The adequacy of monitoring was also examined (Figure 2.1). Blood was taken at 131 of the 141 appointments (93%). Figure 2.2 shows the distribution of tests requested from the 131 samples taken. Vitamins and micronutrients must be ordered separately from biochemistry and haematology requests and as such were analysed independently, being sent in 88 (62%) of reviews. Figure 2.3 details the range of vitamins and micronutrients ordered.

As a subset of this studied group, patients who were newly started on HPN were analysed separately. Ten patients were commenced and remained on HPN in Scotland for at least three consecutive months during 2006. These patients came from four of the seven centres studied. A comparison of HPN indications for these
patients is detailed in Table 2.1. All ten patients met the one hundred day standard on all of their twenty-four clinic appointments during 2006 and each attended an average of 2.4 clinics. Weight was measured at 18 (75%) and anthropometry at 5 of the 24 (21%) assessments. Blood was taken at all 24 (100%) appointments and details of the tests ordered are seen in Figure 2.2 and Figure 2.3. Various combinations of vitamins and micronutrients were measured at thirteen of the twenty-four clinics (54%); only two (8.3%) clinic reviews ordered a complete set of the recommended tests.

Period of HPN treatment was calculated and median averages compared for the three groups, A, B and C (Table 2.1).

We next considered the complications experienced by HPN patients together with the frequency of monitoring in order to establish whether any relationship links increased review interval with increased HPN-related complication rates. For the majority of patients, complications are investigated on an inpatient basis and have no effect on outpatient review appointments. These situations allowed us to look closely at complication rates and scheduled review appointments as independent factors and determine whether closer supervision has any consequence for HPN-related complications and admissions.

Using the same three frequency of review groups, A, B and C, patients were identified who had had complications in 2006 and the three groups compared. Demographics and underlying disease processes were similar in all three groups. (Table 2.1). The complications were divided into HPN-related and disease-related. There were a total
of 34 complications recorded on the Microsoft Access database, which were classified as either HPN-related or disease-related.

Of the fifty-three patients receiving HPN in Scotland in 2006, 16 patients (30%) had at least one complication reported to an HPN team. Examining the total number of complications, Group A had more than double the number of complications of either Group B or Group C. However, when the actual number of patients affected by the complications was investigated, the result was much closer for the three groups, with five patients in Group A, six in Group B and five in Group C. It seems therefore that it is a minority of patients in each group who are each having multiple complications rather than all patients in any one group experiencing problems. The vast majority of complications reported have been classified as HPN-related on the MCN database. Only two patients had both disease- and HPN-related complications over the time period studied, one patient each from Groups B and C.

Statistical analysis was performed using a chi-squared test. Ideally, the authors would have compared HPN complications with both non-HPN complications and no complications in a 3x3 table but with the small numbers involved two cells would have contained either zero or one. In view of this, complications data was grouped into complication v no complication, \( \chi^2 = 0.76 \ p = 0.963 \) and HPN complication v no HPN complication \( \chi^2 = 0.229 \ p = 0.892 \).

Only 3 patients were reported to have had a total of nine disease-related complications between them. These included multiple episodes of small bowel obstruction or
abdominal distension, bleeding from a stoma, a medication related complication, a pulmonary embolus and an episode of intra abdominal sepsis.

Eleven patients experienced 25 episodes of HPN-related complications during 2006, some patients experiencing multiple events during the year. (Table 2.1). Of the HPN-related complications reported, the vast majority were intravenous catheter-related (mostly line infections) but with two episodes of venous thrombosis and three of mechanical failure with broken or split lines. Additionally, there were seven reported cases of metabolic complications, usually dehydration due to inadequate parenteral fluid volume. Three of ten patients reporting line infections were in Group A, three were in Group B and the remaining four were in Group C. It seems unlikely therefore from these observations that frequency of review is important in rate of catheter infection. Although the numbers are very small in this study, there is no obvious difference in the incidence of any HPN-related complication between the three groups. Venous thrombosis associated with the feeding line, mechanical failure and metabolic complications were all reported rarely. For each of these complications, the patients involved were distributed between the three groups and no correlation was apparent between type of HPN-related complication and frequency of review.

Ten patients were newly commenced and remained on HPN in Scotland for at least three consecutive months during 2006. These ‘new’ patients were analysed separately for frequency of review and complication rates. Two new patients had four documented HPN-related complications between them, one having repeated episodes of dehydration, the other a single proven catheter infection.
2.5 Discussion

The British Artificial Nutrition Survey data shows that both point and period prevalence of patients prescribed HPN is increasing year on year, yet little is known regarding the adequacy of monitoring of these patients post-discharge from hospital.

A European multi-HPN centre questionnaire-based study in 2006 concluded that 52% of patients were reviewed at 2-3 monthly intervals once stable with a degree of variation between one and twelve months. Parameters monitored were based on local protocols and often measurements were taken on a ‘when clinically indicated’ basis (Wengler, Micklewright et al. 2006).

In Scotland, the Home Parenteral Nutrition Managed Clinical Network aims to ensure the provision of standardised treatment across a large geographical area without the need to have to centralise treatment to large HPN centres. The MCN has been collecting clinical data on its patients for the past seven years and analysis of this aims to consolidate knowledge of Scottish HPN monitoring as a whole and between centres, ensuring a national guideline is followed and that this guideline is appropriate. The results of treatment in this complete geographical community may be more realistic and true to life than those reported from tertiary referral centres.

Wengler et al studied the monitoring practice of HPN across Europe and concluded that the majority of centres were similar to Scotland in having a monitoring interval for stable patients of 3 months, with a large degree of variation of between 1 and 12 months. In this study, patients discharged on HPN within the last 12 months were identified separately but no comment is made to the frequency of their review interval. It seems that Scotland is in line with the rest of Europe regarding
monitoring frequency but Wengler et al make no comment on complication rates. It is clear from the results of this study that in many cases the targets set by the Scottish HPN MCN are not being met and that a large proportion of patients are not regularly seen within the one-hundred day interval.

There are undoubtedly more reviews that take place on an informal basis, and exceptions where patients are seen elsewhere by healthcare professionals, when patients attend for other clinics or contact the nutrition support team with specific queries. One patient never attends HPN review but has routine bloods, vitamins and micronutrients checked when he attends his renal clinic appointments and consequently meets the target, in frequency if not in content of review. Overall, it can be seen that Scottish patients receiving HPN are not monitored as often or as thoroughly as is recommended by our own guideline. Most importantly, the nutrition support team varies in its skill mix between centres, some benefiting from a dietician and therefore monitoring anthropometry very successfully and others having a biochemist to oversee the bloods, vitamins and micronutrients. One centre, with considerable experience in HPN therapy, has elected to monitor micronutrients and vitamins at six monthly intervals. For these patients, they will appear to breach the recommended intervals for visits but remain very closely and conscientiously monitored. From the centres questioned, it would appear that nutrition clinics do not run every week because this is impractical and therefore if an appointment is missed, it is entirely possible that review will not take place within the guideline of one hundred days as the next clinic will have already been scheduled for several weeks time.
The frequency of review was found to be inversely correlated with the duration of HPN treatment. This might be expected when you consider that it would be instinctive to keep new patients under closer review than the more long-term and presumably stable patients. However, if the guidelines are revisited, no real distinction is made between these two types of patients with regard to monitoring frequency. All new patients were in Group A and the patients with the longest duration of treatment, sometimes many years on parenteral nutrition, tended to be found in Group C, where review frequency was never within one hundred days of the previous clinic appointment. This was not exclusively the case, with some long term and presumably cautious or complicated patients reviewed frequently and some relative new comers managing to be seen far less often. As is seen from the review of complications, no detrimental effect on complication rate was determined by less frequent review.

Examining the content of the review appointments, it was encouraging that weight, arguably the simplest but most informative parameter, was the most frequently monitored of all the components with 86% of all clinic appointments recording this information. Twenty reviews did not measure weight, and twelve of these were from one hospital, perhaps illustrating less robust methods of ensuring weight documentation or an active decision not to weigh all patients at all visits.

The authors believe anthropometry to be an excellent and valuable method of monitoring nutrition status, eliminating concerns over fluid balance and providing a quantitative assessment, when used by experienced personnel to ensure reproducibility. As a somatic measurement, it provides most information when
performed sequentially to monitor changes in nutritional status. Anthropometry was infrequently monitored at all centres yet it and is not known whether this omission was due to a lack of training or equipment. Thirty-four clinic appointments (24%) measured anthropometry, with 21 appointments (62%) of these originating from one hospital benefiting from a dietician being present at all HPN clinic reviews to perform the measurements. Anthropometric data was very much an ‘all or nothing’ occurrence. When measured at review clinics, all three measurements of TSF, MUC and MAC were usually recorded. If a single measurement was made, at clinics not benefiting regularly from a dietician it was TSF that was infrequently recorded. Looking at new patients separately, anthropometry was measured at 21% of appointments. This is a very similar figure to that of the whole group analysis and most likely represents similar problems of lack of training or facilities at these clinics.

As stated in the ESPEN guidelines for HPN (Staun, Pironi et al. 2009) it is recommended that non-nutritional issues including psychological or social problems be monitored and addressed alongside the medical management of HPN patients. The authors recognise and acknowledge the importance of this aspect of continuing patient care. Currently, within the MCN, patient well being, difficulties with equipment or feed and relevant issues of a psychosocial nature are recorded informally on the database within the clinic review/dietetics section. These elements are under investigation by Baxter et al who have produced an HPN-specific quality of life questionnaire to enable routine collection of quality of life data. In view of this pending paper, in part conducted and written by the Scottish HPN MCN manager, it was felt that these elements of review should not be addressed in this research paper.
In the future, it is hoped that the HPN-QOL become part of the routine clinical management of HPN patients (Baxter, Fayers et al. 2009).

One hundred and thirty one of the total 141 clinic visits resulted in blood tests being taken. The results shown in figure 2 indicate that when bloods are taken, urea and electrolytes, liver function tests and full blood counts are very successfully ordered, as would be expected of most follow up appointments. It is of some concern that glucose and CRP were not assessed with the same frequency as both are universally available and yield valuable information in this group of patients. HPN patients may develop impaired glucose tolerance or diabetes and CRP may alert nutrition teams to the presence of sub-clinical infection and is essential if one wishes to interpret the micronutrient levels appropriately.

Vitamin B12 and folate require the filling of two further blood tubes and only half of all clinic appointments measured this component of the nutrition screen. Glucose is also a separate tube to fill. Clinic teams must specifically elect to request and send each of these tests as no predetermined check-list is currently utilised. HPN patients are sometimes difficult to bleed, with chronic conditions leading to poor venous access. Often the small amount of blood obtained must be prioritised for one test at the expense of another. In these situations, and with these variables, choice of tests ordered may vary between centres and nutrition team members, resulting in a different spectrum of tests performed.
HPN patients are at higher risk of bone disease and mineral flux and as such calcium and vitamin D levels should be regularly monitored. Calcium was measured in 72% of cases. Vitamin D was requested on 28% of visits.

The monitoring of vitamins, micronutrients and trace elements is an essential part of clinic reviews in HPN patients, as sub-clinical deficiencies in these substances can result in impairment of immune function and lead to an increased risk of developing a disease process such as infection, neoplastic disease or coronary artery disease (Shenkin 2001). It is apparent from the results (figure 3) that vitamins and micronutrients are usually ordered as a batch or not at all, most having frequencies of between 48% and 60%. The slight variation may be due to irregularities with processing at the laboratory stage. Vitamin C in particular must reach the laboratory within four hours, or it becomes unsuitable for analysis. Another exception is vitamin D, which, as mentioned above, is not part of a ‘micronutrient screen’ and therefore must be specifically requested. The omission of Vitamin D renders the micronutrient screen incomplete in the majority of cases, however as noted above excluding this micronutrient leads to a more satisfactory rate of this aspect of monitoring. It would be interesting to investigate the proportion of these assays that were abnormal, however this data set is incomplete.

It is perhaps reasonable to expect that patients recently commenced on HPN may have a higher rate of complications than those on long term therapy. These results would suggest that new patients do not incur vastly greater numbers of complications than stable patients; however, as all new patients were reviewed within the recommended
time period throughout the year, and therefore in Group A, we are unable to comment on the effect of the regularity of review.

All 10 of the patients newly commenced on HPN during 2006 met the standard regarding monitoring frequency. In only 75% of new patient visits were their weights documented. This is somewhat surprising in view of the difficult fluid balance issues that often surround the commencement of parenteral nutrition. The authors consider the measurement of weight to be helpful and informative as to whether, in the early days of treatment, patients are retaining fluid on HPN and more long term whether they are gaining and maintaining body mass. In the subset of new patient results, one hundred percent of clinic appointments involved blood tests. One hundred percent of patients had UE measured, 96% liver function tests and full blood count. Unfortunately, there was no improvement in glucose monitoring despite these patients all being newly commenced on therapy, but CRP was more frequently monitored in 71% of reviews. Within the new patient subset, micronutrient monitoring was very similar to the whole group findings, and was again largely an ‘all or nothing’ request. In half of the new patients, micronutrients were tested but in only two cases were all nine recommended nutrients measured. When sent, the majority of requests were for all micronutrient and vitamin levels except vitamin D. Interestingly, this group of patients had a much higher percentage of reviews measuring vitamin C. This is difficult to explain, as it is not a parameter that is known to be particularly unstable on commencing HPN, nor is it commonly toxic and therefore there appears to be no reason for this increased surveillance of vitamin C levels in new HPN patients. Perhaps it is the result of better logistics at this subset of
hospitals, where blood samples reach the laboratory more promptly, preserving the ability to measure vitamin C.

To date, there is little evidence as to the consequences of various monitoring regimens for HPN patients. The results of this study do not support an association between review interval and complication rate. Most interestingly, similar numbers of patients in each group were found to have no reported complications, despite the different frequencies of supervision. Looking at the patients reporting complications in the three groups compared with the patients reporting no complications, it was apparent that there was no significant relationship between frequency of review and HPN-related complication rate.

The period of three months as a review frequency for the Scottish HPN MCN patients was set by experts in the field of parenteral nutrition, and approved by NHS Quality Improvement Scotland in 2003. However, from the current study, there may be an argument for increasing the length of time between review appointments, without detrimental effect to patient safety. It may be that nutrition support teams already employ a subconscious two tier system when monitoring their HPN patients, bringing back more unstable patients more frequently. Similarly, patients themselves may be contributing to the apparent failure to meet set standards, electing to attend less frequently when well and with increased frequency when complications arise or following hospitalization. Certainly, from this study the patients seen most often had the highest numbers of HPN-related complications. Formalising this approach and tailoring review to patient needs may be appropriate. There is considerable implication for resources, both financially and in clinical workload and a safe
reduction in the demands of supervision for these patients may be welcomed by those involved in funding and managing this expensive therapy.

This study suggests areas which may be targeted for improvement. The first is the multi professional nature of the review clinics. It is clear that the absence of this team approach can lead to a less comprehensive appraisal of patient progress. The difficulty with achieving this level of review is the high demand on staff for a relatively small group of patients. It may be that more complete sets of blood results would be obtained if each hospital laboratory agreed a list of tests, which would be performed as an “HPN screen” so that there was no need to order the tests individually. However, it is not possible to improve on the poor venous access of most of these long-term patients!

The database contains many incomplete fields at present. Undoubtedly a more complete data set, particularly the dietetics and outpatient review section of the database, would enable an alternative and perhaps clinically superior method of assessing the effectiveness of monitoring standards.

Additionally, the Managed Clinical Network may benefit from the construction of a proforma to provide guidance on essential and desirable components for HPN review clinic appointments. This may ensure that simple informative tests such as weight are more reliably documented and when small amounts of blood obtained, these are directed to the most clinically beneficial tests.
The current study therefore provides more information about current practice in Scotland, seemingly representative of Europe in its monitoring practice, and may serve to generate some much needed evidence base for future refinement of monitoring practice.
2.6 Tables and Figures

Table 2.1
The range of underlying diseases and indications for home parenteral nutrition, the frequency of monitoring and complications in patients receiving HPN in Scotland in 2006 (continued on next page).

Non-Standard Abbreviations: HPN - Home Parenteral Nutrition; NICE - National Institute for Health and Clinical Excellence; MCN - Managed Clinical Network

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Table 2.1 (continued - page 2)
Figure 2.1

**The adequacy of HPN clinic reviews**

The Scottish MCN guideline recommends that an HPN clinic review include biochemical and haematological tests, vitamins and micronutrient level checks, weight measurement and anthropometry.

Non-Standard Abbreviations: HPN - Home Parenteral Nutrition; MCN - Managed Clinical Network
Figure 2.2

Performance of biochemical and haematological tests at HPN clinic reviews as per MCN guideline

Abbreviations: MCN - Managed Clinical Network, HPN - Home Parenteral Nutrition, UE - Urea and electrolytes, LFT - Liver function tests, Glu – Glucose, CRP - C reactive protein, Mg – Magnesium, Ca – Calcium, FBC - Full blood count, FERR - Ferritin
Figure 2.3

Performance of vitamin and micronutrient measurement at HPN clinic reviews as per MCN guideline.

Abbreviations: MCN - Managed Clinical Network, HPN - Home Parenteral Nutrition, B1 - Vitamin B1, B2 - Vitamin B2, B6 - Vitamin B6, C - Vitamin C, D - Vitamin D, Mn – Manganese, Cu – Copper, Zn – Zinc, Se – Selenium, B12/FOL - Vitamin B12/Folate
Chapter 3

Home Parenteral Nutrition in Scotland: Outcome and seven year prospective follow up in a nationwide population

3.1 Introduction

Home Parenteral Nutrition (HPN) plays a crucial and life-saving role in the treatment of patients with intestinal failure. A variety of indications can necessitate parenteral feeding, most commonly short bowel syndrome, but also bowel obstruction, dysmotility, malabsorption or a combination of conditions. Diagnoses include Crohn’s disease, ischaemic bowel, radiation enteritis, malignancy and abdominal trauma.

In Scotland, an important opportunity is provided to review long term survival and HPN dependence across an entire population by the existence of the Scottish HPN Managed Clinical Network (MCN). The network was formed in 2000 and since its creation has collected and recorded prospective data on all patients receiving HPN in Scotland.

Survival data for HPN patients has been reported in multiple case series across the United Kingdom and Europe. Data collected by the British Artificial Nutrition Survey demonstrate 92% one year survival of patients receiving HPN (Jones 2003). Five year survival of patients receiving HPN has been reported from North America and Europe as ranging from 60-79%. (Messing, Crenn et al. 1999; Vantini, Benini et al. 2004; Jeppesen, Staun et al. 1998; Scolapio, Fleming et al. 1999; Lloyd, Vega et al. 2006; Pironi, Forbes et al. 2008; Lloyd, Zabron et al. 2008) (25-29, 31, 57).
Previous studies have identified factors associated with prognosis to include residual small bowel length (Messing, Crenn et al. 1999), age at initiation of HPN (Vantini, Benini et al. 2004; Jeppesen, Staun et al. 1998), underlying primary diagnosis (Vantini, Benini et al. 2004; Jeppesen, Staun et al. 1998) and HPN dependency (Vantini, Benini et al. 2004).

To date, studies have generally reported on either single centre experiences or those of tertiary referral centres where large numbers of highly selected intestinal failure patients are treated. Through the existence of the MCN, we are able to report the survival rates and outcomes of HPN patients across the whole of Scotland, where treatment is delivered locally under nationally agreed guidelines by each hospital possessing an appropriately constituted Nutrition Team who are members of the Scottish HPN network. As a result of the network and the consequent availability of HPN across this wide geographical area, we are provided with this diverse demographic to consider.

This study aims to establish whether this population of patients behave in a similar way to previously reported groups in terms of survival, prognostic factors and HPN dependence. Unusually, perhaps uniquely, all patients included in the study have been followed and their data entered prospectively since commencement of their parenteral nutrition.
3.2 Methods

All patients receiving HPN funded by the NHS in Scotland are known to the MCN through ongoing contact between the established centres and the Network Manager. In addition there is constant publicity about the network to hospitals not involved, and there are regular reports from the commercial company providing the HPN service to the network. This report includes all patients on HPN in Scotland from January 2000 until the censor date of 31st December 2007.

Data was collected from the purpose-built *Microsoft Access* database, completed prospectively by nutrition teams at all HPN MCN centres. Missing or queried data were resolved by one of the researchers (NH) contacting the local nutrition team, and via case note review. Data collected included age at commencement of HPN, gender, diagnosis and mechanism of intestinal failure necessitating HPN, duration on treatment (calculated from the date of discharge from hospital on HPN), patient mortality including cause of death and ongoing HPN dependence. HPN dependence was taken as an ongoing requirement for parenteral nutrition for greater than two years following discharge, or until either death or withdrawal from HPN due to poor prognosis. Reasons for stopping HPN treatment were also noted. For the majority, this was death or treatment withdrawal for poor prognosis, or recovery / surgical intervention/bowel adaptation. Several patients progressed to enteral nutrition, and in a small group, HPN was withdrawn for a miscellany of other reasons.
3.3 Statistical analysis
All patients who commenced HPN prior to the formation of the MCN were excluded from the data, leaving an entire group of HPN patients with purely prospective results. All patients were followed up until 31st December 2007. Minitab was used to analyse the outcome data. Kaplan-Meier survival analysis was used to calculate the overall probability of survival and 1, 3 and 5 year survival rates. Median survival time was also calculated. Patients surviving until the censor date and remaining on HPN were then analysed, with respect to diagnosis using the Log Rank test. The overall difference was calculated as was the difference between each pair of diagnoses. In addition, age at first discharge was analysed by plotting against date of first discharge.
3.4 Results

The study covers the eight-year period from January 2000 to December 2007. Throughout the study period, 136 patients received HPN under the care of the Scottish MCN. This equates to 17 new cases per year. Duration of treatment totalled 271 patient years and averaged 2 years, with a range of one month to 8 years. The median age for new patients was 47 years, with a range of 16 to 80 years. The commonest age range for new patients was 41 – 59 years, accounting for 53% of all new patients commenced on HPN therapy (Table 3.1). Twenty one percent of patients were in the oldest age group. A single patient was referred to Hope Hospital Salford in 2003 and has been followed up there by his own preference. He has only been referred for follow up in Scotland in 2010 and is therefore not included in our data set.

Table 3.1 Demographic data for 136 HPN patients

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<thead>
<tr>
<th>Characteristic</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (34)</td>
</tr>
<tr>
<td>Female</td>
<td>90 (66)</td>
</tr>
<tr>
<td>Age at start of HPN treatment</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>36 (26.5)</td>
</tr>
<tr>
<td>41-59</td>
<td>72 (52.9)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>28 (20.6)</td>
</tr>
</tbody>
</table>
Table 3.2 Diagnoses within the study

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s</td>
<td>46 (34)</td>
</tr>
<tr>
<td>Ischaemic Bowel</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Motility</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Radiation Enteritis</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (25)</td>
</tr>
</tbody>
</table>

The commonest diagnosis amongst the patients was Crohn’s disease, accounting for 34% of the group. Twenty percent of patients had a diagnosis of ischaemic bowel disease and eight percent had a malignancy. Four patients, accounting for 3%, had radiation enteritis and a quarter of all patients had a miscellany of ‘other’ diagnoses, including chronic pancreatitis, sclerosing peritonitis, post surgical complications, hypoganglionosis, and visceral hypersensitivity (Table 3.2).

Differences in the distribution of patients with respect to age at which treatment started, the duration of treatment and when in the study they commenced HPN were assessed and are summarised in Figures 3.1, 3.2 and 3.3.

In Figure 3.1, age at initiation of HPN was plotted with respect to diagnosis. Each pair of diagnoses were compared using a t-test; Table 3.3 shows the resulting p-values. Patients with Crohns disease were significantly younger at time of initiation of HPN than patients with ischaemia or ‘other’ diagnoses. Patients with ischaemia were also significantly older than those with motility disorders and ‘other’ diagnoses.
Table 3.3  Age at diagnosis. Comparison between disease groups (p values). t-test

<table>
<thead>
<tr>
<th>START AGE</th>
<th>Ischaemia</th>
<th>Motility</th>
<th>Malignancy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohns</td>
<td>&lt;0.001 **</td>
<td>0.190</td>
<td>0.036</td>
<td>0.006 *</td>
</tr>
<tr>
<td>Ischaemia</td>
<td></td>
<td>0.010 *</td>
<td>0.646</td>
<td>0.047 *</td>
</tr>
<tr>
<td>Motility</td>
<td></td>
<td></td>
<td>0.199</td>
<td>0.285</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td>0.499</td>
</tr>
</tbody>
</table>

Figure 3.3 shows the distribution of duration of treatment with respect to diagnosis. A Mann Whitney u test was used to test pairs of diagnoses for significance as this data set is non-parametric. Table 3.4 shows resulting p values. The only significant difference observed in this group was seen on comparison of patients with ischaemia and those with motility disorders, with the ischaemia group having a shorter duration of treatment.

Table 3.4  Duration of Treatment. Comparison between disease groups (p values).

Mann-Whitney test

<table>
<thead>
<tr>
<th>DURATION</th>
<th>Ischaemia</th>
<th>Motility</th>
<th>Malignancy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohns</td>
<td>0.554</td>
<td>0.056</td>
<td>0.729</td>
<td>0.329</td>
</tr>
<tr>
<td>Ischaemia</td>
<td></td>
<td>0.027 *</td>
<td>0.949</td>
<td>0.985</td>
</tr>
<tr>
<td>Motility</td>
<td></td>
<td></td>
<td>0.093</td>
<td>0.019</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td>0.920</td>
</tr>
</tbody>
</table>

In Figure 3.3, the patient groups were plotted with respect to date of commencing HPN to evaluate indications for treatment over the study period. A t-test was used to examine significance (Table 3.5). Patients with ‘other’ diagnoses commenced HPN
significantly later within the study period than patients with malignancy. No other significant differences were observed between groups.

Table 3.5  HPN start date. Comparison between disease groups (p values). t-test

<table>
<thead>
<tr>
<th>START DATE</th>
<th>Ischaemia</th>
<th>Motility</th>
<th>Malignancy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohns</td>
<td>0.711</td>
<td>0.293</td>
<td>0.138</td>
<td>0.233</td>
</tr>
<tr>
<td>Ischaemia</td>
<td></td>
<td>0.441</td>
<td>0.266</td>
<td>0.155</td>
</tr>
<tr>
<td>Motility</td>
<td></td>
<td></td>
<td>0.887</td>
<td>0.086</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td>0.023 *</td>
</tr>
</tbody>
</table>

Table 3.6  Indications for HPN within this study

<table>
<thead>
<tr>
<th>Indication for HPN</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Short gut</td>
<td>74 (54)</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Fistula</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Gastric hold up</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sclerosing peritonitis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (20)</td>
</tr>
</tbody>
</table>

Over half of all patients (54%) had a short gut as their indication for HPN. Other indications included obstruction, malabsorption, fistulae, malnutrition, gastric hold up, sclerosing peritonitis and a collection of more obscure reasons, labelled ‘other’ which
included protein losing enteropathy, visceral myopathy and oesophageal dysfunction (Table 3.6).

Of the 136 patients in the group, forty seven patients (35%) were still receiving HPN on the censor date of 31st December 2007. Thirty four patients (25%) had died and fifty five patients (40%) had stopped receiving HPN for reasons other than death, no longer requiring the therapy. These reasons included recovery (51%), bowel adaptation (22%), surgical intervention (25%) such as bowel re-anastomosis or closure of fistulae and one patient who stopped for undocumented reasons (2%).

Figure 3.4 shows the outcome of all patients at the censor date. Figure 3.5 shows the break down of reasons for discontinuing HPN treatment in those patients labelled ‘stopped HPN’ in Figure 3.4. Half of these patients recovered, were weaned successfully and no longer needed parenteral nutrition, one quarter had gastrointestinal surgery, 22% underwent bowel adaptation, and a small percentage had other reasons for termination of treatment. All patients in this group stopped HPN to reinstate enteral nutrition.

3.4.1 Mortality

There were a total of 34 deaths in the study group. These are detailed in Table 3.7. The majority, twenty two patients (65%) who died during the study period had disease related causes of death. Only four patients (12%) had pure HPN related deaths and a further two patients (6%) had deaths attributed to a combination of disease and HPN. HPN related deaths were due to either sepsis or liver disease.
Table 3.7  Cause of death of patients on HPN

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Patients</th>
<th>Median months on HPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPN related</td>
<td>4</td>
<td>4.5</td>
</tr>
<tr>
<td>Disease related</td>
<td>22</td>
<td>10.5</td>
</tr>
<tr>
<td>Combination</td>
<td>2</td>
<td>17.5</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>25</td>
</tr>
</tbody>
</table>

‘Other’ includes;

- metastatic breast cancer
- sepsis
- lung cancer
- myocardial infarction
- acute myeloid leukaemia

Fifty five patients had stopped HPN due to reasons other than death (Table 3.8).

Table 3.8  Reasons for stopping HPN

<table>
<thead>
<tr>
<th>Reason</th>
<th>Patients</th>
<th>Median months on HPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Surgery</td>
<td>14</td>
<td>5.5</td>
</tr>
<tr>
<td>Bowel adaptation</td>
<td>12</td>
<td>12.5</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>
Other includes one patient with co-morbidities, multiple line infections and a mutual decision between HPN team and patient not to continue HPN.

### 3.4.2 Survival analysis

The overall survival probability after starting HPN for the 136 patients studied was 86.0% at 1 year, 81.6% at 2 years, 78.7% at 3 years, 77.2% at 5 years and 76.5% at 6 years (Figure 3.6).

For Figure 3.7, patients who stopped HPN for reasons other than death have been removed. The plot shows survival in those who died on HPN and those who were still receiving HPN at the censor date. This gives the survival plot for all patients who during the study period died on HPN or continued it until the end of the study.

Survival distribution by diagnosis is shown in Figure 3.8. Log rank test showed the overall differences in survival to be significant at p<0.001. P<0.05 was taken as significant. Probability of survival was therefore influenced by disease diagnosis. Table 3.9 shows the p values for each pair of diagnoses. Significant differences were found between Crohn’s disease and ischaemia, ischaemia and motility disorder and ischaemia and ‘other’ diagnoses. A highly significant difference was found between survival in Crohn’s disease and malignancy, motility disorder and malignancy and malignancy and ‘other’ diagnoses.
Table 3.9  All patients: Survival grouped by disease - Log-Rank comparisons

<table>
<thead>
<tr>
<th></th>
<th>Ischaemia</th>
<th>Motility</th>
<th>Malignancy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s</td>
<td>0.009 *</td>
<td>0.136</td>
<td>0.001 **</td>
<td>0.910</td>
</tr>
<tr>
<td>Ischaemia</td>
<td></td>
<td>0.006 *</td>
<td>0.295</td>
<td>0.011 *</td>
</tr>
<tr>
<td>Motility</td>
<td></td>
<td></td>
<td>0.001 **</td>
<td>0.121</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td>0.001 **</td>
</tr>
</tbody>
</table>

Survival was assessed with respect to age at initiation of treatment (Figure 3.9). Patients were grouped into those who started HPN aged <40yrs (n=36), 40-59yrs (n=72) and >60yrs (n=28) and survival at 5 years was calculated for each group. The overall log rank p value is 0.957. Five year survival for each group is 82.7, 76.0 and 74.1 % for the three groups respectively.

Figure 3.10 plots the survival of the HPN patients by their time of starting treatment. The 136 patients have been divided into Group 0, those commencing HPN 2003-2005, Group 1, who commenced treatment in 2000-2002, and Group 2, for patients starting treatment on or after 2005. Log rank comparisons of each pair of groups show no significant difference between starting HPN in any of the three time periods (Table 3.10).

Table 3.10  Survival grouped by time starting HPN. P=0.537 Log-Rank comparisons between groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 0</td>
<td>0.671</td>
<td>0.502</td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
<td>0.262</td>
</tr>
</tbody>
</table>
Patients from the two centres providing HPN to the largest numbers of patients in Scotland were extracted and their survival plotted against patients from all other Scottish centres. There was no difference between these two groups p=0.518 (Figure 3.11).

3.4.3 Home Parenteral Nutrition dependence analysis

In this study dependence on HPN was 61%, 51% and 48% at 1, 3 and 5 years (Figure 3.12).

Additionally, 49 cases (89%) of the 55 cases where PN was weaned successfully happened within two years of commencing therapy. Of the 44 patients not weaned off HPN within 2 years, only a subsequent 6 patients (14%) were successfully weaned from HPN to other forms of nutrition and 86% were classified as having permanent intestinal failure. Of the six patients who managed to stop HPN after more than 24 months of therapy, 4 were classified as having undergone bowel adaptations and 2 as recovered from the cause of intestinal failure.
3.5 Discussion

The Scottish Managed Clinical Network oversees the care of all patients in Scotland who are receiving Home Parenteral Nutrition. This arrangement provides a unique opportunity to follow the outcome of a geographically diverse and complete HPN population over a number of years. Data collection in this study is entirely prospective. The MCN was set up in 2000 and all patients commenced on HPN prior to this have been removed from the study. Patients starting treatment from this time onwards have been included to ensure demographic and clinical data is accurate and reliable.

3.5.1 Patient demographics

As in the national data, there is a trend for new patients to be in the older age group of 60+ years (Jones 2007; Elia, Russell et al. 2001). The age distribution of patients reflects that of the national data, with the commonest age range for new patients being 41-59 years. Patient demographics and diagnoses were similar to previous studies with the exception of the percentage of patients receiving HPN for malignancy, which is far fewer in this Scottish study and the UK in general when compared with patient prescriptions for HPN in North America (Scolapio, Fleming et al. 1999). Additionally, no patients in this current study were given HPN for an HIV-related disorder, illustrating a geographical difference in practice.

3.5.2 Underlying disease processes

The most common diagnosis leading to the prescription of HPN was Crohn’s disease, (34%), followed by ischaemic bowel (20%). This is comparable with the British Artificial Nutrition Survey (BANS) data (Jones 2007). Also consistent with the
BANS report (Jones 2007) is the miscellany of ‘other’ diagnoses which make up a large proportion of HPN patients in both studies. This is thought to be due to a heterogenous group of diagnoses - mainly surgical complications - necessitating parenteral nutrition, but could also be due to inconsistencies in classifying patients’ diagnoses on the database. Worldwide there are differences in the use of HPN. Inflammatory bowel disease is a much less common indication for HPN prescription in other parts of the world, with 11% of patients in North America (North American Home Parenteral and Enteral Nutrition Registry 1994 1992), and a minor percentage of all HPN cases throughout Asia (Wang, Wu et al. 2007). In mainland Europe, the United States, and Asia a far greater proportion of HPN patients have a cancer diagnosis than in the UK. Italian nutrition teams prescribe 88% of their HPN for malignancy (Violante, Alfonsi et al. 2006). In America, 42% of HPN is for cancer patients (North American Home Parenteral and Enteral Nutrition Registry 1994 1992), in Japan the proportion is 40% 93 and in Taiwan it is over 70% (Wang, Wu et al. 2007). In Scotland, this study finds only 8% of HPN prescription to be for patients with a primary diagnosis of malignancy. Evidently, there remains much controversy and a lack of agreement internationally regarding the prescription of HPN. This disparity presumably reflect large national differences in philosophic and economic viewpoints. The management of patients with malignancy in the UK rarely includes the use of parenteral nutrition. The insurance funded medical care in the USA may influence the numbers of cancer patients treated with this high maintenance therapy. Previous work shows cancer patients to have similar readmissions for HPN related complications but four times as many for disease related ones (Howard 1992).
Italian studies deem HPN in terminal cancer patients to be a safe and effective treatment (Violante, Alfonsi et al. 2006). Across Europe opinions are divided and the questions remain as to whether nutritional support improves the survival of patients with cancer or allows the patient to feel better and have an improved quality of life?’ (Bozzetti 1995). Cancer patients with a diagnosis of malignancy generally fall into three broad groups; those with the iatrogenic malnutrition as a consequence of treatment of cancer, those with active cancer whose treatment is hindered by disease related malnutrition and those in the terminal phase with concurrent intestinal failure. It is with the terminal diagnosis of malignancy that most controversy remains and utilisation of this provision varies most from country to country. HPN appears to be a valid intervention in terminal patients whereby death would be secondary to malnutrition rather than the spread of malignant disease. It is obviously ethically unacceptable to randomise patients to either starvation or non-starvation and as such no quantitative data is available to strengthen arguments for the use of HPN in terminal patients. Quality of life data would support HPN use with the aim of prolonging functionality as long as individual patient specific endpoints are identified to determine whether or not goals are accomplished and therefore whether to withdraw treatment.

Demographic data were studied to investigate any temporal relationships or differences between diagnosis groups. Over the years, there has been a broadening of the age range of patients starting HPN. Only two categories of diagnoses contained patients that started their treatment before the age of thirty. As would be expected, most young patients using HPN had a diagnosis of Crohn’s disease, where complications requiring parenteral nutrition can occur at any time. One patient
commenced HPN just before his sixteenth birthday having developed small bowel fistulae to an ileostomy. The rest of the patients who started HPN relatively young were in the ‘other’ diagnosis group, with diagnoses ranging from Systemic Lupus Erythematosus with gastric hold up, to chronic pancreatitis and chronic pseudo-obstruction. In the older age range at which patients were given HPN, ischaemic bowel and malignancy featured most commonly, although a single Crohn’s patient commenced treatment in his seventieth year and motility disorders and ‘other’ diagnoses also had patients of this age group beginning their therapy.

Comparing pairs of diseases, Crohn’s disease was found to be significantly different to ischaemic bowel $p<0.01$, to malignancy $p=0.036$ and to the other diagnosis group, $p=0.006$ with respect to age of commencing therapy. Ischaemic bowel was also significantly different to motility disorder, $p=0.01$ and other diagnosis, $p=0.047$ groups. This has been examined in previous studies. Howard et al 1995 (Howard, Ament et al. 1995) looked at outcome in HPN patients in North America. Diagnostic groups of Crohn’s disease, ischaemic bowel and motility disorders were pooled and outcome compared in paediatric, middle age and geriatric groups, concluding that although outcome was better in the younger age group over several outcome measures, including nutrition status at one year, complication rate and rehabilitation status, it was good in all three groups and age per se should not prevent patients receiving treatment. Co-morbidities and simply older age may affect survival. The diagnosis of ischaemic bowel occurs mainly in the older age group and has a somewhat poorer survival so consequently often results in a shorter duration of treatment. But old age alone does not preclude treatment. Younger patients had better survival rates on therapy, a greater likelihood of resuming full oral nutrition
after 1 year, and more complete rehabilitation than older patients. The only negative factor for paediatric patients was their more frequent readmission for HPN-related sepsis compared with adult subjects. Geriatric adults receiving HPN did not experience more therapy related complications than their middle-aged counterparts (Howard, Ament et al. 1995). Perhaps it could be speculated that older age patients commenced on HPN would be more highly selected than disease equivalent younger patients.

### 3.5.3 Duration of HPN treatment

Figure 3.2 concerns duration of treatment and showed the majority of patients to be receiving relatively short term treatment with HPN i.e. 12-18 months for all diagnoses except motility disorder, for which patients duration of treatment was more varied - some with only a year or 2 of treatment and an approximately equal number receiving 6, 7 or 8 years of treatment. Overall, this probably relates to the nature of the disorder, with acute Crohn’s exacerbations, fistulae, or the short term treatment of malignant sequelae requiring spells of intravenous feeding, as compared to disorders of bowel motility, which are usually non-rectifiable requiring long term parenteral nutrition more frequently. Ischaemia was significantly different in its duration of treatment to that of motility disorders. This probably relates to the other cardiovascular complications which often accompany a patient with this diagnosis.

### 3.5.4 Diseases treated with HPN over the study period

Diagnoses were plotted with respect to time from beginning of study to examine any changing practice over the eight years (Figure 3.3). The range of diagnoses for which HPN is given has not altered significantly in the last eight years in Scotland. This is
comparable to United Kingdom data from the BANS report which compares 2000 and 2006 new registrations, and point prevalence (Jones 2007). In both the current Scottish study and the UK wide data, Crohn’s disease remains the predominant diagnosis (Jones 2007). The number of ‘other diagnoses’ is on the increase in more recent years, with a cluster of new ‘other diagnoses’ commenced on treatment in the last 4 years in the current study. This agrees with the BANS data (Jones 2007), and in both studies probably reflects an increasing number of patients who experience complications in complex surgical cases where the temporary or permanent outcome is a requirement for parenteral nutrition.

3.5.5 Indications for treatment

The principal indication for HPN in this study was short bowel syndrome (SBS) as was the case in previous studies (Messing, Crenn et al. 1999, Vantini, Benini et al. 2004; Lloyd, Vega et al. 2006). SBS usually results from repeated resection of small bowel strictures due to Crohn’s disease but can also result from extensive small bowel resection as a consequence of superior mesenteric artery / vein thrombosis or volvulus (Lal, Teubner et al. 2006; Irving 2000). A UK based study showed that the cause of intestinal failure in the majority of their patients with Crohn’s disease was multiple unplanned laparotomies and that a far smaller percentage of Crohn’s disease patients acquired short bowel syndrome through either extensive disease or uncomplicated sequential resections (Agwunobi, Carlson et al. 2001). Other indications included bowel obstruction, small bowel fistulae and malabsorption. Bowel obstruction is often secondary to malignancy, which is an infrequent indication for parenteral nutrition in Scotland (5% in this study) yet is the commonest indication for HPN in Italy (Buchman, Moukarzel et al. 1994) and North America (North American Home
Parenteral and Enteral Nutrition Registry 1994 1992). Differences in indications or diagnoses between centres and countries will inevitably have implications when survival data is interpreted. Of note, no patients in this current study had an underlying diagnosis of AIDS, which mirrors the pattern of decline in the prescription of HPN for this disease in all countries except Belgium, where 35% of patients at one centre had AIDS as their underlying disease (Van Gossum, Bakker et al. 1999).

3.5.6 Mortality
There were a total of 34 deaths in the study group. These are detailed in Table 3.7. The majority, twenty two patients (65%) who died during the study period had disease related causes of death. Only four patients (12%) had pure HPN related deaths and a further two patients (6%) had deaths attributed to a combination of disease and HPN. HPN related deaths were due to either sepsis or liver disease.

Death was as a consequence of disease in the majority of patients in the current study. Details on the HPN MCN database surrounding individual patient deaths are vague and in the majority a single drop down menu choice is applied for cause of death. It is known that both HPN related liver disease and HPN related sepsis were causative in the death of four patients in this study. Patients dying of disease related complications had a longer median duration of HPN therapy than those with HPN related deaths. It could be postulated therefore that in the short term, death is more likely a consequence of HPN related problems but as a patient continues on therapy, their cause of death is much more likely to be attributable to their underlying disease process.
3.5.7 Outcomes

Overall, the outcomes for the study population at the censor date was death in 25% of patients, whilst 35% of patients remained on HPN treatment and 40% stopped HPN due to improvement of condition or surgical intervention (Figure 3.4). The group of patients who stopped HPN are represented in Figure 3.5. Looking specifically at the patients who were able to stop HPN, 51 percent of this group recovered sufficiently from conditions where temporary HPN was required, either to rest the bowel, allow for fistulae healing or combat malnutrition. Twenty-one percent underwent bowel adaptation, whereby their remaining gut adjusted to perform all necessary roles and thereby remove the need for parenteral nutrition. One quarter of all patients who managed to stop intravenous feeding had surgical intervention to re-anastomose the bowel. The literature does not contain many comparisons for this data, although a retrospective Italian study in 2002 found 51% of patients to still require HPN treatment at the end of analysis, 25% of patients were dead and 12.5% were successfully weaned from HPN. A single patient underwent intestinal transplantation and a further 3 patients (7.5%) were followed by other centres (Pironi, Paganelli et al. 2003).

Survival probabilities throughout the follow up period are comparable with previous studies. The 5 year survival probability of 77.2% may be compared with those of 73% (Lloyd, Vega et al. 2006), 75% (Messing, Crenn et al. 1999) and 78.6% (Vantini, Benini et al. 2004). The studies included in table 3.11 include two non-malignant populations, (Messing, Crenn et al. 1999 and Pironi, Paganelli et al. 2003). Despite many European studies reporting malignancy as a common diagnosis treated with HPN, table 3.11 lists studies in which there is minimal representation of this
behaviour. The UK study (Lloyd, Vega et al. 2006) and the current Scotland study both include patients with malignancy but local practices keep these numbers low. On this basis, it is therefore not valid to surmise that HPN positively influences survival in malignancy.

**Table 3.11** Comparison of the survival probabilities throughout follow up within the literature, including the current study (Scotland)

<table>
<thead>
<tr>
<th></th>
<th>1 yr</th>
<th>2 yr</th>
<th>3 yr</th>
<th>5 yr</th>
<th>6 yr</th>
<th>10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lloyd, Vega et al. 2006)</td>
<td>86%</td>
<td>77%</td>
<td>73%</td>
<td></td>
<td></td>
<td>71%</td>
</tr>
<tr>
<td>(Pironi, Paganelli et al. 2003)*</td>
<td>97%</td>
<td>82%</td>
<td>67%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Vantini, Benini et al. 2004)</td>
<td>95%</td>
<td>93%</td>
<td>88%</td>
<td>79%</td>
<td></td>
<td>65%</td>
</tr>
<tr>
<td>(Messing, Crenn et al. 1999)*</td>
<td>94%</td>
<td>86%</td>
<td>75%</td>
<td></td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td><strong>Scotland</strong></td>
<td><strong>86%</strong></td>
<td><strong>82%</strong></td>
<td><strong>79%</strong></td>
<td><strong>77%</strong></td>
<td><strong>77%</strong></td>
<td><strong>-</strong></td>
</tr>
</tbody>
</table>

* = non malignant study group

When considering survival data the influence of the underlying disease must be recognized. Different case series are likely to be influenced by the differences in the patient groups studied, and by whether or not the case series contains patients with a diagnosis of malignancy. The closest comparison study in terms of study size and case mix in the literature shows very similar overall survival rates at 1, 3 and 5 years (Lloyd, Vega et al. 2006). Differences in survival are apparent when diagnosis groups are compared. Kaplan-Meier analysis shows significantly lower survival in subjects with malignancy and gut ischaemia when compared with the other groups of motility disorders, Crohn’s disease and other diagnoses (Table 3.12). There are no
significant differences in survival between motility disorders, Crohn’s disease and other diagnoses, or between malignancy and gut ischaemia.

Table 3.12  Probability of survival (Kaplan-Meier) by disease indication

<table>
<thead>
<tr>
<th></th>
<th>Yr 1</th>
<th>Yr 2</th>
<th>Yr 3</th>
<th>Yr 4</th>
<th>Yr 5</th>
<th>Yr 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motility</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Other</td>
<td>90.2</td>
<td>85.4</td>
<td>85.4</td>
<td>85.4</td>
<td>85.4</td>
<td>85.4</td>
</tr>
<tr>
<td>Crohn’s</td>
<td>92.7</td>
<td>88.6</td>
<td>86.3</td>
<td>86.3</td>
<td>86.3</td>
<td>86.3</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>74.1</td>
<td>66.6</td>
<td>62.9</td>
<td>55.5</td>
<td>55.5</td>
<td>55.5</td>
</tr>
<tr>
<td>Malignancy</td>
<td>72.7</td>
<td>54.5</td>
<td>54.5</td>
<td>45.5</td>
<td>45.5</td>
<td>36.4</td>
</tr>
</tbody>
</table>

Underlying disease was associated with probability of survival in this study. As would be expected, subjects with Crohn’s disease had a better prognosis than those with ischaemia or malignancy (Table 3.13). The estimated 5 year survival (86.3% 95% C.I. 73.3-96.5%) results are comparable with similar studies - 87% C.I 74-94% 29, 75% C.I. 67-83% 25, 92% 28.
Predictably, survival was poor in patients with underlying malignancy, with all but one patients who died having disease related deaths. Survival was also poorer in patients with bowel ischaemia, although for a disease renowned for its poor prognosis, perhaps 55% survival at five years is reasonably encouraging. This diagnosis comprises both venous and the more common arterial disease. The frequency of clinical manifestations of atherosclerosis in Great Britain - and the West of Scotland in particular - is especially high. Our patient group is likely to contain a high proportion of patients with marked atheromatous disease, leading to arterial bowel infarction and a worse prognosis, as has been seen in previous studies (Messing, Crenn et al. 1999; Scolapio, Fleming et al. 1999). Lloyd et al quoted a better prognosis with ischaemic bowel patients and attributes this to a higher percentage of patients having venous pathology (Lloyd, Vega et al. 2006). Motility disorders had a 100% five year survival in this current study, but by comparison, in the study by Lloyd et al 2006 (Lloyd, Vega et al. 2006), survival was much worse in this group, approximately 55%. A possible explanation might be the variation in the classification of patients into disease groups between studies. The current study

Table 3.13  Probability of survival (Kaplan-Meier) by disease indication at 5 years with 95% confidence intervals

<table>
<thead>
<tr>
<th></th>
<th>Yr 5</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motility</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>85.4</td>
<td>74.5 – 96.1</td>
</tr>
<tr>
<td>Crohn’s</td>
<td>86.3</td>
<td>73.3 – 96.5</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>55.5</td>
<td>36.3 – 74.3</td>
</tr>
<tr>
<td>Malignancy</td>
<td>45.5</td>
<td>16.0 – 74.8</td>
</tr>
</tbody>
</table>
classified systemic sclerosis into a group of ‘other’ diagnoses, whereas the Lloyd study (Lloyd, Vega et al. 2006) categorises these patients as dysmotility disorder, consequently worsening survival statistics in this group.

Little is found in the literature to address whether patients commenced on treatment earlier in the study period have differing survival rates to those who started treatment at a later date. The current study found that survival during this relatively short time period was similar regardless of when therapy was commenced. Similarly, but over a longer study duration, a previous study found that the decade of commencing HPN did not affect survival (Lloyd, Vega et al. 2006). It is likely that the three time periods are not sufficiently chronologically distinct to show any differences in outcome dependent on date of commencement, however it is also possible that survival probabilities have plateaued until further treatment developments are made.

Unlike previous studies (Messing, Crenn et al. 1999; Vantini, Benini et al. 2004; Scolapio, Fleming et al. 1999; Pironi, Paganelli et al. 2003) a younger age at initiation of HPN in this study did not show a significant survival advantage. Jeppesen et al showed mortality was twice as high in patients aged over 50yrs (34%) as in younger patients (18%) (Jeppesen, Staun et al. 1998). Lloyd et al found a significant relationship between patient age at commencement of HPN and survival, with an almost threefold risk of death in patients starting HPN at >55yrs compared with those starting at <54yrs (Lloyd, Vega et al. 2006). It may not be valid to draw too many conclusions from the current study as our group numbers in both the under forty and over sixty years were small in comparison with previous reports. However, the similarity of our survival data for all three age groups was striking (p=0.957).
Possible explanations may include a population with less severe disease or less co-morbidity. Additionally, the current study has a low proportion of cancer diagnoses - a disease more common later in life and a likely explanation for poor survival in these older age groups if high numbers of malignancy diagnoses are present. This does not however account for differences from the Lloyd study which also contains relatively few cancer patients.

The two centres who oversee the largest numbers of HPN patients in Scotland are Glasgow Royal Infirmary and Ninewells Hospital, Dundee. Both have patients with more than ten years of HPN treatment. Treatment with HPN in Scotland is facilitated through the Managed Clinical Network; it is not the intention to centralise care but to allow treatment to be delivered in the nearest hospital via adoption of national standards, guidelines and protocols (Scottish Home Parenteral Nutrition Managed Clinical Network). This allows equity of access and standardised treatment across a challenging geographical area. Survival at these two large centres was compared with the combined outcome for all other Scottish centres. Reassuringly, there was no difference in survival between these two groups (p=0.518). This adds weight to an already strong argument for managing patients with a multi professional team approach and provides support to the existence of this Network, suggesting patient outcome is similar regardless of location within Scotland.

3.5.8 HPN dependence

Dependence on parenteral nutrition was calculated and compared with previous reported figures (Table 3.14). HPN dependence in this study was broadly comparable to that of a French study which is entirely comprised of consecutive non-
malignant adult short bowel patients from two centres monitored by an official regional HPN centre (Messing, Crenn et al. 1999). This is a similar set up to the current Scottish study, with comparable monitoring and patient demographics. In contrast, the strikingly different proportions of patients remaining HPN dependent in the Lloyd study (Lloyd, Vega et al. 2006) probably reflects the selection of complex patients referred to a tertiary centre.

Table 3.14  HPN dependence

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Messing et al 1999 *</td>
<td>53%</td>
<td>49%</td>
<td>-</td>
<td>45%</td>
</tr>
<tr>
<td>Lloyd et al 2006</td>
<td>89%</td>
<td>-</td>
<td>87%</td>
<td>84%</td>
</tr>
<tr>
<td>Jeppesen et al 1998</td>
<td>-</td>
<td>53%</td>
<td>-</td>
<td>75%</td>
</tr>
<tr>
<td>Scotland</td>
<td>61%</td>
<td>53%</td>
<td>51%</td>
<td>48%</td>
</tr>
</tbody>
</table>

* = non malignant short bowel syndrome group

In the current study, 89% of patients with transient intestinal failure (IF) were weaned from HPN after 24 months, and an 86% of patients with greater than 24 months treatment went on to be classified as having permanent IF. In the previous study by Lloyd et al (Lloyd, Vega et al. 2006), the equivalent figures were 95% and 94% respectively. One explanation for our patients not stopping HPN as early as in previous similar studies may be that when patients are doing well clinically they may miss clinic appointments, or are reviewed slightly less often than patients with more clinical need. This may delay the decision to attempt weaning until beyond the 24-month point. Of the patients who successfully weaned from HPN after more than 24 months, half (3 patients) had a diagnosis of Crohns disease, and consequent short bowel syndrome. These patients took an average of 43 months to achieve adequate
bowel adaptation, supporting suggestions that adult bowel adaptation can occur after 1-3 years of HPN (Nightingale, Lennard-Jones et al. 1992).

The first monoclonal antibody treatment for Crohns disease was introduced just prior to the start of the current study and this method of treatment may well have influenced outcome data specifically related to HPN patients with a diagnosis of Crohns disease. The successful treatment of recurrent and fistulating Crohns disease patients using Infliximab, Adalimumab or equivalents has undoubtedly enabled patients who previously would have remained parenterally fed to return to an enteral route of nutrition through these efficacious new therapies (van Deventer 1999). More recently, the CHARM study (Crohn’s Trial of the fully human antibody adalimumab for remission maintenance) examined the efficacy of adalimimab for long-term maintenance in remission Crohn’s disease and concluded that adalimumab had a significantly lower rate of hospitalisation and surgery at one year than placebo (Feagan, Panaccione et al 2008). Anti TNF therapies have also been found to be effective in the treatment of severe active Crohns disease (CLASSIC-I trial) (Hanauer, Sandborn 2006). These developments may result in fewer patients acquiring short bowel syndrome secondary to surgical intervention and lessen the need for HPN in future years.

3.5.9 Conclusions

In conclusion, the five year survival of patients receiving HPN in this study was 77.2%. This equals the five year survival in the Lloyd study (Lloyd, Vega et al. 2006), which centred on a tertiary referral centre for intestinal failure. However, the
current study is an entirely prospective study, lending additional weight to the quality and reliability of data. It also provides interesting information on how a complete geographical population receiving HPN behaves. Age was not found to be predictive of survival in our study, and this may just be that our numbers were too small to show any differences.

This study aimed to encompass all patients receiving HPN Scotland wide. Towards the end of the analysis period a single patient who resides in Scotland but chooses to receive HPN monitoring from an English IF centre was located. As he has never featured in our monitoring process, and is not counted in our survival statistics, we are able to accept and except him from this study and still draw conclusions on a population. However, this development illustrates the difficulties in ensuring a whole population data is captured for analysis.

HPN dependence in this study mirrored that of a French study, with just under half of all patients still dependent on HPN at five years. Much higher percentages of patients remain HPN dependent in other recent studies, the reason for this is unclear but probably relates to the mix of patients involved, their range of underlying diseases and complexity of their cases. It is also worth considering how a patient is deemed HPN independent, and whether it is more frequent reviews or smaller numbers at individual centres which provoke the nutrition team to contemplate whether a patient is ready or able to be weaned from treatment.

Also encouraging for our Managed Clinical Network is the lack of survival difference between the two largest bases for HPN monitoring (Glasgow Royal Infirmary and
Ninewells Hospital Dundee) versus the rest of the nutrition centres across Scotland. It is certainly the intention of the Network to provide an equivalent service to all HPN patients irrespective of geographical location and this result supports an achievement of this and a obligation to continue with this essential supervision of therapy.

Finally, and with a view to future work, a study is only as good as the data entered and in retrospect, some aspects of the Scottish HPN MCN database, from which all data has been gathered may benefit from improvement. Accuracy is obviously a priority when compiling outcome date. Drop down menus and free text boxes leave room for error and interpretation regarding such information as reason for stopping HPN and cause of death. Additionally, many patients have either a diagnosis or indication for HPN listed as ‘other’. Although this is sometimes necessary in individualised complex surgical cases, addressing this issue by either educating the persons responsible for data input or completion of a formal proforma at the time of commencing treatment with HPN may reduce this ‘other’ category and further improve data accuracy.
Figure 3.1

Age at Initiation of HPN by diagnosis. Grey dots represent individuals. Blue cross represents mean. Error bars 95% CI for the Mean

n=136
Figure 3.2

Duration of HPN treatment by diagnosis. Grey dots represent individuals. Blue cross represents mean. Error bars 95% CI for the Mean

n=136
Figure 3.3

HPN starting date by disease. Grey dots represent individuals. Blue cross represents mean. Error bars 95% CI for the Mean

n=136
Figure 3.4

Outcome at censor date

n=136
Figure 3.5

The break down of reasons for discontinuing HPN treatment in those patients labelled ‘stopped HPN’ in Figure 3.4
Figure 3.6

Kaplan Meier Survival Plot - All patients

n=136
Figure 3.7

Kaplan Meier Survival Plot

Survival in those who died on HPN / those who were still receiving HPN at the censor date

n=81
Figure 3.8

Kaplan Meier Survival Plot - All patients

Survival grouped by disease

n=136
Figure 3.9

Kaplan Meier Survival Plot – All Patients

Survival grouped by age at initiation of HPN

n=136
Figure 3.10

Kaplan Meier Survival Plot – All Patients

Grouped by time starting HPN

n=136
Figure 3.11

Kaplan Meier Survival Plot – All Patients

Grouped by location. Dundee / Glasgow Royal Infirmary vs other centres

n=136
Figure 3.12

HPN dependence over time (all patients)

n=136
Chapter 4

Manganese levels in patients receiving HPN from a single Scottish tertiary referral centre

4.1 Introduction

Manganese (Mn) is considered an essential trace element which is required as an activator in many enzymatic reactions. Patients receiving long-term parenteral nutrition are provided with Mn as part of a trace element solution which is added to their intravenous feed. Differing preparations of multiple trace elements contain various amounts of Mn but further than this, refinement of daily dose is currently extremely difficult and crude. Patients are prescribed HPN either with or without one of these fixed dose supplements.

Manganese absorption from the gastrointestinal tract is inversely correlated to dietary content. Children and infants absorb more than adults and females appear to absorb more than males. In the healthy adult, 5% of orally ingested Mn is absorbed and hypermanganesaemia is not a concern (Hardy, Hardy et al. 2008). Elimination of manganese predominantly occurs through the hepatobiliary system and intestinal absorption is vital in manganese homeostasis. In parenterally fed patients, this control is lost; Mn is 100% bioavailable resulting in a risk of hypermanganesaemia.

The suspicion that cholestasis may play a role in hypermanganesemia originates from the knowledge that the liver is the primary organ involved in Mn uptake and excretion. Cholestatic liver disease is a well recognized complication of total parenteral nutrition and with Mn undergoing biliary excretion, liver disease can lead to hypermanganesaemia. In addition, some studies have suggested that Mn may be
causal in cholestasis, with reduction or withdrawal of Mn from feed correlating with a decrease in both bilirubin and aspartate aminotransferase (AST) and in one report experimentally infused manganese induced an intrahepatic cholestasis (Ayotte, Plaa 1985). In 1990, Mehta et al reported a woman who was receiving Mn-supplemented parenteral nutrition for 4 months presenting with a cholestatic jaundice and an extrapyramidal syndrome associated with high blood manganese levels. Two years later, Ejima et al reported details of a man who received 23 months of HPN and developed no cholestatic jaundice, yet was found to have an accumulation of manganese in the basal ganglia giving rise to Parkinsonism (Mehta, Reilly 1990; Ejima, Imamura et al. 1992). Following these observations, Fell et al examined children receiving parenteral nutrition and concluded that a complex relationship existed between hypermanganesaemia and cholestasis, with both abnormalities able to influence the existence of the other. Levels of inflammatory markers have also been linked to levels of Mn in patients, with one study finding that Mn levels correlated with Erythrocyte Sedimentation Rate (ESR), and Tumour Necrosis Factor α (TNF α) (Reimund, Dietemann et al. 2000).

Cumulative Mn dose has also been suggested to be relevant in patients found to be hypermanganesemic. Post mortem studies of cumulative Mn dosing showed high levels of manganese in patients’ tissues, especially those with liver and renal disease, and Howard et al (Howard, Ashley et al. 2007) suggest manganese, like copper, should be removed as an additive when liver-associated enzymes rise to twice normal.

With the exception of experimentally induced cases, a single isolated clinical case of a short-bowel patient with Mn deficiency has been reported, where the deficiency was
successfully corrected with oral supplementation (Norose, Terai et al. 1992). In contrast; long-term HPN patients are frequently reported as being hypermanganesaemic. Excess Mn has led to neurological symptoms of hyperirritability and extrapyramidal disease in children. These neurological symptoms correlated with increased signal intensity in the basal ganglia on magnetic resonance imaging (MRI) (Fell, Meadows et al. 1996; Reynolds, Blumsohn et al. 1998). MRI abnormalities slowly disappeared after manganese supplements were stopped. Additionally, liver dysfunction improved once manganese supplementation was withdrawn from HPN (Fell, Meadows et al. 1996). A study of post mortem manganese levels showed a cumulative effect of long term supplementation (Howard, Ashley et al. 2007). Regular monitoring of patients receiving fixed doses of Mn over prolonged periods is recommended (Baxter 2009). No satisfactory indicator of whole body Mn has to date been identified and neither plasma nor serum levels is felt to provide an accurate representation of levels. As the majority of Mn is contained in red blood cells, Reynolds et al suggest that whole blood Mn concentrations are deemed the most reliable and reproducible monitoring parameter (Reynolds, Blumsohn et al. 1998). In agreement with this, Hardy recently stated that whole-blood levels are more accurate for monitoring and they correlate well with signal intensity of magnetic resonance imaging (Hardy 2009).

Many reports have documented the existence of hypermanganesaemia in HPN patients (Wardle, Forbes et al. 1999; Reimund, Dietemann et al. 2000; Hardy, Hardy et al. 2008; Siepler, Nishikawa et al. 2003). The Scottish HPN MCN provides the opportunity to examine the behaviour of Mn levels in chronic parenteral nutrition patients monitored closely at a tertiary referral nutrition centre. As manganese
deficiency is virtually unknown in humans and there is growing evidence for toxicity if levels are high, any information regarding factors contributing to hypermanganesemia is valuable in understanding how to avoid excessive concentrations and identifying patients potentially at risk of toxicity as well as questioning whether it is necessary to add Mn to parenteral nutrition at all.

This study aims to elucidate any relationship between WBMn levels and variables such as hepatic function, inflammation and cumulative Mn dose. It also aims to determine whether WBMn level relates specifically and predictably to dose in the past 7, 14, 21, 28, 56 and 84 days.
4.2 Methods

All patients receiving HPN funded by the NHS in Scotland are known to the MCN through ongoing contact between the established centres and the Network Manager. This report includes all patients receiving long term HPN from Glasgow Royal Infirmary during 2007. Long term is defined as greater than 12 months of treatment. All patients are monitored in accordance with the Scottish Home Parenteral Nutrition Managed Clinical Network (HPNMCN) recommended guidelines. These advise that long-term HPN patients undergo regular micronutrient and trace element monitoring. Guidelines are based on expert opinion as, to date, little evidence base is available regarding frequency or content of HPN patient monitoring. Currently, regular review infers three-monthly blood tests. Blood was taken at clinic visits and sent to the Central Trace Element Laboratory which is based at Glasgow Royal Infirmary. In addition, other blood tests were taken and sent for analysis as is part of any routine outpatient visit to the HPN clinic. Together with other monitoring and clinical data, these results are entered into a purpose built Microsoft Access database, which is completed prospectively by members of the nutrition team at the HPN MCN centre.

All measurements of whole blood manganese were extracted from the database and missing or queried data resolved by one of the researchers (NH) contacting the local nutrition team and the central trace element laboratory at Glasgow Royal Infirmary. Other concurrent data collected included patient demographics, duration of HPN treatment, type and dose of trace element preparation prescribed and any changes in manganese prescription. The two trace element preparations in use were Additrace which provided 1mg per dose and Decan which provided 0.04mg per dose. Additionally, where measured, ferritin (Ferr), alkaline phosphatase (ALP) and C
reactive protein (CRP) measurements corresponding to whole blood Mn (WBMn) levels were extracted.

Individual patient whole blood manganese levels were extracted from the data set and average levels calculated for enforced times of 100, 500 and 1000 days post commencement of HPN. Enforced times were generated by averaging all available levels of manganese and times of measurement for each individual patient into more comparable time periods i.e. all bloods taken within the first 100 days were averaged to give enforced time 100 and enforced Mn level 100 etc. Similarly, alkaline phosphatase units/l, C reactive protein mg/litre and ferritin ng/ml levels were taken from the same time periods. Cumulative Mn dose and consequently average Mn dose per day were also calculated for each patient.
4.3 Statistical Analysis

Values for whole blood Manganese, ALP, CRP and ferritin were extracted from the Microsoft Access database as described above. Correlations were tested using Matlab. A Spearman correlation was performed, giving a correlation coefficient (R) and a p-value. Initial testing showed a number of significant correlations between measured whole blood Mn and doses administered during the time-frame of interest. Correlations were repeated removing data points at which the dose on Mn during the time-frame of interest was zero, as these points were significantly skewing the data, producing significant associations from very few (occasionally 1) non-zero Mn dose data points.
4.4 Results

4.4.1 Manganese levels within this study group

In the first part of the study investigation concerned with manganese levels in individual patients and their relationships to manganese dose, liver function and markers of inflammation, a total of twelve patients had had sufficient time on HPN and sufficient clinic visits with blood tests to analyse their data. Three patients were not included in this initial part of the study, two were not on HPN for an adequate duration (less than 1000 days) and one had had very few available blood test results to analyse. With 12 patients and 3 time periods, a total of 36 Mn levels were possible (Table 4.1). Three levels were not measured. Eleven of the 12 (92%) patients recorded abnormally high Mn levels at least once, 5 patients at all three time points. Twenty-five of 33 (78%) Mn levels were abnormal and 13 (41%) of these were greater than twice normal levels (70-280nm/l). Individual patient whole blood Mn levels relative to the normal range are shown in Figure 4.1.

<table>
<thead>
<tr>
<th>Enforced Time (days)</th>
<th>Pt 1</th>
<th>Pt 2</th>
<th>Pt 3</th>
<th>Pt 4</th>
<th>Pt 5</th>
<th>Pt 6</th>
<th>Pt 7</th>
<th>Pt 8</th>
<th>Pt 9</th>
<th>Pt 10</th>
<th>Pt 11</th>
<th>Pt 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>134</td>
<td>286</td>
<td>411</td>
<td>-</td>
<td>630</td>
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<td>639</td>
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<td>566</td>
<td>196</td>
<td>373</td>
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<tr>
<td>500</td>
<td>322</td>
<td>207</td>
<td>1303</td>
<td>312</td>
<td>530</td>
<td>724</td>
<td>773</td>
<td>445</td>
<td>405</td>
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<tr>
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<td>317</td>
<td>338</td>
<td>300</td>
<td>281</td>
<td>199</td>
<td>167</td>
<td>478</td>
<td>-</td>
</tr>
</tbody>
</table>

4.4.2 Comparison of manganese level to other blood parameters

Figures 4.2 – 4.4 show plots of whole blood Mn level v ALP, CRP, ferritin at time periods 100 days, 500 days and 1000 days.
In each case, reducing Mn dosage or stopping it completely resulted in a trend towards normal range Mn levels but overall there was no significant difference in WBMn levels over the three time periods. \( p = 0.236 \). Neither CRP nor ferritin levels varied significantly over the time periods however ALP measurements were significantly different \( p = 0.013 \).

### 4.4.3 Comparison of manganese levels with cumulative manganese dose

Figure 4.5 shows whole blood Mn v cumulative Mn dose at the three time periods. An initial plot shows no obvious relationship between calculated cumulative Mn dose and WBMn level for any of the three enforced time periods.

In the second part of the analysis, the population studied was all 15 patients who were receiving HPN under the care of the Glasgow Royal Infirmary nutrition team on 31/12/2007. Average age at the start of treatment was 59 years, with 5 male patients and 10 females. The majority had a diagnosis of Crohns disease. They had all been on HPN at least one year, with a median duration of 4.9 years of treatment (Table 4.2).
Table 4.2 GRI HPN patient demographics.

<table>
<thead>
<tr>
<th>patient</th>
<th>gender</th>
<th>age at start</th>
<th>diagnosis</th>
<th>duration tx to date (yrs)</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>57.6</td>
<td>crohns disease</td>
<td>5.90</td>
<td>renal dysfunction</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>56.5</td>
<td>crohns disease short gut following surgery for benign condition</td>
<td>6.52</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>67.28</td>
<td>short gut following surgery for benign condition</td>
<td>5.83</td>
<td>liver dysfunction</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>51.23</td>
<td>crohns disease fistula following surgery</td>
<td>9.76</td>
<td>renal dysfunction</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>56.63</td>
<td>crohns disease fistula following surgery</td>
<td>6.03</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>52.54</td>
<td>crohns disease fistula following surgery</td>
<td>7.13</td>
<td>renal dysfunction</td>
</tr>
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<td>7</td>
<td>f</td>
<td>49.8</td>
<td>crohns disease fistula following surgery</td>
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<td>osteoporosis</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>15.93</td>
<td>crohns disease fistula following surgery</td>
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<td>f</td>
<td>54.45</td>
<td>motility disorder fistula following surgery</td>
<td>3.38</td>
<td>osteoporosis, protein losing enteropathy</td>
</tr>
<tr>
<td>10</td>
<td>f</td>
<td>41.63</td>
<td>crohns disease fistula following surgery</td>
<td>15.01</td>
<td>renal dysfunction</td>
</tr>
<tr>
<td>11</td>
<td>f</td>
<td>62.87</td>
<td>ischaemia fistula following surgery</td>
<td>3.74</td>
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</tr>
<tr>
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<td>crohns disease fistula following surgery</td>
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<td>m</td>
<td>40.56</td>
<td>sclerosing peritonitis fistula following surgery</td>
<td>2.47</td>
<td>renal dysfunction</td>
</tr>
<tr>
<td>15</td>
<td>f</td>
<td>54.61</td>
<td>malignancy fistula following surgery</td>
<td>1.71</td>
<td>none</td>
</tr>
</tbody>
</table>

4.4.4 Cumulative manganese dose

No relationship was demonstrated between cumulative dose and WBMn. When Mn levels are plotted using symbol coding to identify each patient separately, no relationship is found within either intra or inter patient data (Figure 4.6).
Table 4.3 Correlation coefficients and p values for each patient between cumulative Mn dose and WB Mn level

<table>
<thead>
<tr>
<th>patient</th>
<th>R values</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2741</td>
<td>0.2561</td>
</tr>
<tr>
<td>2</td>
<td>-0.399</td>
<td>0.0814</td>
</tr>
<tr>
<td>3</td>
<td>-0.5672</td>
<td>0.0544</td>
</tr>
<tr>
<td>4</td>
<td>-0.0947</td>
<td>0.7271</td>
</tr>
<tr>
<td>5</td>
<td>-0.633</td>
<td>0.0085</td>
</tr>
<tr>
<td>6</td>
<td>-0.1371</td>
<td>0.6402</td>
</tr>
<tr>
<td>7</td>
<td>-0.4877</td>
<td>0.0553</td>
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<tr>
<td>8</td>
<td>-0.2991</td>
<td>0.4718</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
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<td>0.588</td>
</tr>
<tr>
<td>12</td>
<td>-0.9801</td>
<td>0.0034</td>
</tr>
<tr>
<td>13</td>
<td>-0.2056</td>
<td>0.5687</td>
</tr>
<tr>
<td>14</td>
<td>0.2369</td>
<td>0.609</td>
</tr>
<tr>
<td>15</td>
<td>-0.5702</td>
<td>0.3156</td>
</tr>
</tbody>
</table>

Correlation between manganese dose in the previous 7, 14, 21, 28, 56 and 84 days and whole blood Mn level was investigated. Data was skewed by the presence of large numbers of data points at which a blood Mn level was measured, but there had been no Mn dosing during the prior time period of interest. P values resulting from correlation testing including these zero values is shown in Table 4.4. The results of correlation testing following the removal of these zero-value data points are shown in Table 4.5.
Table 4.4 p values following correlation between Mn dose in time period specified and measured Mn level

<table>
<thead>
<tr>
<th>Patient</th>
<th>7 days</th>
<th>14 days</th>
<th>21 days</th>
<th>28 days</th>
<th>56 days</th>
<th>84 days</th>
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<tbody>
<tr>
<td>1</td>
<td>0.037</td>
<td>0.034</td>
<td>0.033</td>
<td>0.033</td>
<td>0.02</td>
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</tr>
<tr>
<td>2</td>
<td>0.009</td>
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<td>0.002</td>
</tr>
<tr>
<td>3</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>4</td>
<td>0.001</td>
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<tr>
<td>5</td>
<td>0.001</td>
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<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>6</td>
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<td>0.414</td>
<td>0.421</td>
<td>0.424</td>
<td>0.448</td>
<td>0.536</td>
</tr>
<tr>
<td>7</td>
<td>0.192</td>
<td>0.179</td>
<td>0.237</td>
<td>0.367</td>
<td>0.61</td>
<td>0.698</td>
</tr>
<tr>
<td>8</td>
<td>0.315</td>
<td>0.323</td>
<td>0.326</td>
<td>0.327</td>
<td>0.329</td>
<td>0.331</td>
</tr>
<tr>
<td>9</td>
<td>0.001</td>
<td>0.001</td>
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</tr>
<tr>
<td>10</td>
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<td>0.016</td>
<td>0.016</td>
<td>0.017</td>
<td>0.029</td>
<td>0.037</td>
</tr>
<tr>
<td>11</td>
<td>0.017</td>
<td>0.017</td>
<td>0.017</td>
<td>0.017</td>
<td>0.017</td>
<td>0.017</td>
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<tr>
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<tr>
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<td>0.125</td>
<td>0.125</td>
<td>0.031</td>
<td>0.018</td>
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<td>14</td>
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<td>0.001</td>
<td>0.001</td>
<td>0.008</td>
<td>0.001</td>
<td>0.002</td>
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<td>15</td>
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<td>0.961</td>
<td>0.961</td>
<td>0.961</td>
<td>0.961</td>
</tr>
</tbody>
</table>

Table 4.5 p values following correlation between Mn dose in time period specified and measured Mn level, following removal of data points in which the Mn dose during the specified time period was zero.

<table>
<thead>
<tr>
<th>Patient</th>
<th>7 days</th>
<th>14 days</th>
<th>21 days</th>
<th>28 days</th>
<th>56 days</th>
<th>84 days</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.813</td>
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<td>0.084</td>
<td>0.027</td>
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<tr>
<td>3</td>
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<td>0.473</td>
<td>0.473</td>
</tr>
<tr>
<td>4</td>
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<td>no value</td>
</tr>
<tr>
<td>5</td>
<td>0.12</td>
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<td>0.12</td>
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<td>0.12</td>
</tr>
<tr>
<td>6</td>
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<td>0.46</td>
<td>0.46</td>
<td>0.46</td>
<td>0.753</td>
<td>0.622</td>
</tr>
<tr>
<td>7</td>
<td>0.192</td>
<td>0.179</td>
<td>0.237</td>
<td>0.367</td>
<td>0.61</td>
<td>0.698</td>
</tr>
<tr>
<td>8</td>
<td>0.315</td>
<td>0.323</td>
<td>0.326</td>
<td>0.327</td>
<td>0.329</td>
<td>0.331</td>
</tr>
<tr>
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</tr>
<tr>
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<td>no value</td>
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<td>13</td>
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<td>no value</td>
</tr>
<tr>
<td>14</td>
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<td>no value</td>
<td>no value</td>
<td>no value</td>
</tr>
<tr>
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<td>no value</td>
<td>no value</td>
<td>no value</td>
<td>no value</td>
<td>no value</td>
</tr>
</tbody>
</table>
4.5 Discussion

Numbers are small in this study of a single tertiary centre and this fact must be acknowledged prior to interpretation and discussion of results. There is undoubtedly a high incidence of high WBMn levels amongst our patients. In individual cases, this is responsive to a decrease in Mn dosage or the omission of Mn supplementation from intravenous feed. Although levels fell in response to dose alteration, they very often remained high months later at the next three monthly micronutrient screening. Perhaps Mn continues to be released from high level tissue stores for an unknown duration following dose adjustment.

The high manganese levels cannot be adequately explained by changes in inflammatory markers or liver dysfunction as there was no significant correlation with markers of either. The lack of relationship between cumulative dose and WBMn in the first part of this study is maintained in the second part where it is examined more closely by calculating correlation coefficients for each patient. The results show a lack of correlation between these variables. In retrospect, given that each analysis point includes data from the preceding analysis point, it is questionable whether this section of the study concerning cumulative dose is statistically valid.

Manganese dose in the previous 7, 14, 21, 28, 56 and 84 days were examined with respect to WBMn levels. It was postulated that one of these time periods may show a positive relationship to WBMn level and that it would be clinically useful to be able to state that the dose in the preceding x days is most relevant and predictive of Mn level. This data was skewed by the presence of large numbers of data points at which a blood Mn level was measured, but there had been no Mn dosing during the prior time
period of interest. Correlation testing including these zero values gave a high number of significant positive correlations, even in cases where there were very few non-zero values (Table 4.3). Correlation testing following the removal of these data points at which no Mn had been given during the period of interest showed only a single significant association at 84 days in a single patient. It can therefore be concluded that there is no clinically useful correlation between Mn dosing and Mn level during the time frames investigated. It may also be questioned whether it is valid to draw conclusions from this analysis, as the Mn dose at each time period also includes the doses from previously analysed shorter time periods and is therefore not an independent variable. Additionally, the latter patients whose Mn levels were monitored with respect to their cumulative and 7, 14, 21, 28, 56 and 84 day doses had few monitoring dates, each having been receiving HPN for relatively short amounts of time.

In this study manganese levels did not correlate with either cumulative dose of Mn, recent dose of Mn or cholestasis. This is in agreement with previous studies (Wardle, Forbes et al. 1999), and suggests that factors other than manganese excretion and manganese dosage may be responsible for blood levels of the trace element. Oral intake in this study was not quantified but it is informally known that most patients involved in this study take some degree of enteral nutrition. It is possible that oral plus parenteral manganese provision may have some bearing on the high WBMn levels recorded. Wardle et al (Wardle, Forbes et al. 1999) and Siepler et al (Siepler, Nishikawa et al. 2003) agree that this is a valid possibility yet a difficult factor to quantify. Tea and leafy vegetables are rich sources of manganese (Reynolds, Blumsohn et al. 1998) and in this current study no attempt to document the specifics
of oral intake was made. This may have been a useful addition to the data collected and should certainly be considered for future work.

Apart from inappropriately high dosages, Mn contamination of intravenous products is a concern. For more than 20 years studies from the United States have shown that PN solutions without Mn supplementation can contain 5–38 ng/L, especially from calcium gluconate, magnesium sulphate, or potassium chloride (Pluhator-Merton, Fedorak et al. 1999). The reports of Mn contamination have been so widespread over the years that there is no doubt there is a problem that needs to be addressed by manufacturers (Hardy 2009). Manganese is also present in the needles and tubing used to acquire and process blood samples and this, together with the unreliability of dosage secondary to contamination from what is officially manganese-free parenteral nutrition makes it even more difficult to ensure consistent intake and support a cautious approach to prescribing this metal.

In previous studies, hypermanganesemia has correlated with abnormal MRI scans in the patients concerned, brain Mn storage being very slowly cleared from cerebral mitochondria even when parenteral Mn supplementation is discontinued (Alves, Thiebot et al. 1997; Mirowitz, Westrich et al. 1991). However, none of the patients scanned in these studies exhibited clinical signs of extrapyramidal disease or psychosis (Bertinet, Tinivella et al. 2000). It is not disputed that a method of monitoring to prevent Mn accumulation is highly necessary in HPN patients. However, routine MRI is not a feasible option and the search for an accurate and reliable marker of Mn build up continues.
In conclusion, patients in the current study have demonstrable hypermanganeseemia, in line with HPN patients from many previous studies. This study aimed to address this observation, and confirm or refute some possible causes. However, from the outset it was noticeable that Mn concentrations differed wildly between patients and no clear dose-response was evident. Later in the study and also concerning was the plan to draw conclusions from measurements which contained subsets of the same data with respect to dose in the past 7, 14, 21, 28, 56 and 84 days; each longer period also encompassing the shorter periods analysed before.

What can be concluded is that no association was found between whole blood Mn level and either alkaline phosphatase, C reactive protein or ferritin at any of the three enforced time periods. In addition, in both parts of the study, and despite the various forms of analysis used, no correlation was demonstrated between cumulative Mn dose and WBMn level. Finally, no correlation was demonstrated between dose over time periods examined and WBMn level. Other possible causes of Mn accumulation which have previously been raised and have not to date been excluded include dietary intake and Mn contamination of intravenous nutrition. It is still possible that either of these variables may be clinically relevant or in fact the result is multifactorial and many of the above mentioned factors play some role in hypermanganeseemia. One last possibility is that we have not identified the most relevant marker of tissue Mn and this may be key to elucidating a more clinically useful relationship.

Regarding Mn supplementation in HPN patients; with increasing data showing high levels of WBMn and the scarcity of Mn deficiency, together with the difficulties experienced in monitoring Mn experienced to date, it may be relevant and prudent to
consider the possibility of discontinuing the routine use of manganese supplementation in patients requiring long term parenteral feeding.
**Figure 4.1**

Individual patient whole blood Mn levels related to normal range.
Figure 4.2

Whole blood Manganese vs ALP, CRP and Ferritin at 100 days
Figure 4.3

Whole blood Manganese vs ALP, CRP and Ferritin at 500 days
Figure 4.4

Whole blood Manganese vs ALP, CRP and Ferritin at 1000 days
Figure 4.5

Whole blood Mn v cumulative Mn dose at the three time periods (100, 500 and 1000 days)
Figure 4.6

The relationship between measured whole blood Mn and log cumulative Mn dose.

All data points for all patients. Individuals differentiated by colour.
Conclusions

Home Parenteral Nutrition remains the core treatment for patients with intestinal failure. In Scotland, the HPN Managed Clinical Network plays a crucial role in ensuring the provision of the therapy to all appropriate patients. It also facilitates local monitoring of patients and makes possible audit and research projects aiming to further enhance understanding and improve treatment with respect to chronic intestinal failure.

In chapter one, the monitoring of Scottish HPN patients was investigated and compared with the recommended standards for frequency and content of review. Only one third of patients consistently met the set standard of review frequency yet no relationship was found between other patients reviewed less often and any increase in frequency of complication requiring hospitalisation. This finding may go some way to providing support for reduced frequency in review of this type of patient. To qualify this, and notably, patients seen more often in this study had a few more recorded HPN related complications, inferring that there may be some informal decisions to more closely follow those with stormier courses of treatment. Formalising this approach may of course benefit the already overstretched NHS both financially and in clinical workload.

Content of review appointments was on the whole encouraging. Improvements can and should be made in simple areas such as weight measurement, a crucial parameter in nutrition patients. Over and above this, the skill mix of the nutrition team varies between centres and this is evident from biochemical and anthropometric data. This
is a more difficult problem to standardise but education of team members and a written proforma to guide a clinic review may be of some benefit.

Chapters 2 and 3 again benefit from the data of an entire geographical population. Survival and HPN dependence statistics were acquired for Scottish HPN patients and were broadly comparable with those of a tertiary UK referral centre for Intestinal Failure. This is encouraging for the MCN who strive to provide the same level of care as the main IF centres over a wide area, with multiple teams and in numerous distant settings. Patient deaths were in the main disease related, and diagnosis was significant in predicting outcome in line with other recent studies. HPN dependence was acceptable and in fact less at five years than in the tertiary centre, probably reflecting a different mix of pathology and perhaps a smaller centre approach to the constant consideration of patient suitability for weaning. Anecdotally, some centres have more of a surgical slant to management of IF than others, and comparison of our Scottish data to this type of institution would prove interesting. Heartening was the comparison of two larger HPN centres to the rest of the Scottish HPN bases and the demonstration of no difference in outcome, strengthening the success of the Network. Recommendations from this study would include improvement of the database itself, to promote accuracy and detail in documentation of complication and mortality data.

The last chapter concerns manganese analysis in the Scottish HPN population. It is true to say that, as in many other reported studies, our patients are frequently hypermanganesemic, yet remain clinically asymptomatic and with to date, little demonstrable relationship between manganese prescription and measured whole blood Mn level. From the outset, and with initial crude analysis of results, no
correlation was evident between these two variables. Some patients received Mn doses orders of magnitude greater than others and had normal Mn measurements, with other receiving minimal doses and still achieving hypermanganesemic states. In retrospect, perhaps these results should have raised questions regarding the usefulness of pursuing this line of investigation. Formal analysis of cumulative Mn dose versus Mn level again showed no correlation and validity of the figures is debatable when each dose is deemed not to be independent, being influenced by all previous doses. No explanation for high Mn levels was found in other blood parameters, and it is probable that a highly complex relationship exists between multiple influences to produce hypermanganesemia. Uncertainty exists as to the measurable form in which Mn most accurately behaves as a biomarker of the whole body content. Whole blood, plasma and red cell Mn have all been suggested to represent tissue levels. However, to date, and with such a definite lack of relationship between dose and response so far, perhaps obtaining tissue levels of HPN patients at opportune times e.g. operative intervention may further elucidate the behaviour of Mn dosing at tissue level and provide some guidance to its influences. Lastly, in the knowledge that clinical hypomanganesemia is almost unknown and dietary and contamination routes can both provide small quantities of the trace element, perhaps the next step in addressing this nutritional dilemma is to examine levels in HPN patients receiving no formal manganese prescription with the hypothesis that its addition may be superfluous.

The current study has examined a small amount of the data potentially available from the MCN. This data provides a unique resource in terms of the inclusion of the generality of HPN patients rather than the selected population of a tertiary referral centre. Future work and further potential studies would include a closer look at HPN
feed prescriptions, the behaviour of liver enzymes in HPN patients, analysis of the MCN anthropometric data and detailed investigation of other trace elements recorded in the Scottish HPN MCN which can be easily accessed through their central processing at Glasgow Royal Infirmary.
References


HANAUER, S.B., SANDBORN, W.J., RUTGEERTS, P., FEDORAK, R.N., LUKAS, M., MACINTOSH, D., PANACCIONE, R., WOLF, D., POLLACK, P.


intestinal and multivisceral transplantation at Addenbrooke's hospital, Cambridge University. Poster presentation; British Association of Parenteral and Enteral Nutrition